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(54) **SUBSTITUTED TETRAHYDRONAPHTHALENES, PROCESS FOR THE PREPARATION THEREOF AND THE USE THEREOF AS MEDICAMENTS**

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USPC **514/613**; 514/317; 514/646; 514/656; 546/112; 546/192; 546/195

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USPC 514/317, 646, 656, 613; 546/112, 192, 546/195
See application file for complete search history.

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(57) **ABSTRACT**

The invention relates to substituted tetrahydronaphthalenes and derivatives thereof, and also to the physiologically compatible salts and physiologically functional derivatives thereof, to preparation thereof, to medicaments comprising at least one inventive substituted tetrahydronaphthalene or derivative thereof, and to the use of the inventive substituted tetrahydronaphthalenes and derivatives thereof as medicaments.

19 Claims, No Drawings

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SUBSTITUTED TETRAHYDRONAPHTHALENES, PROCESS FOR THE PREPARATION THEREOF AND THE USE THEREOF AS MEDICAMENTS

This application is a Continuation of International Application No. PCT/EP2008/006700, filed Aug. 14, 2008, which is incorporated herein by reference in its entirety.

The invention relates to substituted tetrahydronaphthalenes and derivatives thereof, and also to the physiologically compatible salts and physiologically functional derivatives thereof, to preparation thereof, to medicaments comprising at least one inventive substituted tetrahydronaphthalene or derivative thereof, and to the use of the inventive substituted tetrahydronaphthalenes and derivatives thereof as medicaments.

Compounds which have pharmacological action and whose overall structure is similar to the substituted tetrahydronaphthalenes and derivatives thereof described in the present application are already described in the prior art, for example in WO2002/064565 and WO 2000/051970.

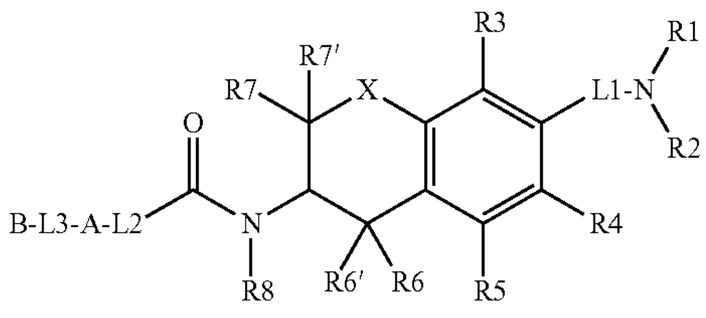
WO2008/002575, WO2008/001160, WO2006/044293, WO2005/033063, US2005/0075324, US 2006/0247239 and Meyers K. M. et al., Bioorganic & Medicinal Chemistry Letters 17, 2007, 814-18; Meyers K. M. et al., Bioorganic & Medicinal Chemistry Letters 17, 2007, 819-22; Mendez-Andino J. L. et al., Bioorganic & Medicinal Chemistry Letters 15, 2007, 2092-2105 disclose amino-substituted tetrahydronaphthalene derivatives with MCH R1-antagonistic action for treatment of obesity.

Further compounds with MCH-antagonistic action for treatment of obesity have been described in the prior art (examples: WO2005047293, WO2004092181, WO2005103039, WO2004024702, WO2001021577, WO2003035624, WO2002089729, WO2002006245, WO2002002744, WO2002057233, WO2003045313, WO2003097047, WO2002010146, WO2003087044, WO2003/087046, WO2001/021577). A review is given in Rokosz, L. L., Expert Opin. Drug Discov. 2007, 2, 1301-1327.

It was an object of the invention to provide compounds which bring about weight reduction in mammals and which are suitable for prevention and treatment of obesity and diabetes and their manifold sequelae.

Surprisingly, a series of compounds which modulate the activity of MCH receptors has been found. More particularly, the compounds feature antagonism of MCH R1.

The invention therefore relates to compounds of the formula I



I

in which

R1, R2 are each independently H, $(C_1$-$C_8)$-alkyl, $(C_1$-$C_4)$-alkoxy-$(C_1$-$C_4)$-alkyl, $(C_3$-$C_8)$-alkenyl, $(C_3$-$C_8)$-alkynyl, CO(R9), $(C(R10)(R11))_q$-R12, $CO(C(R13)(R14))_r$-R15, CO—O$(C_1$-$C_8)$-alkyl, $CO(C(R13)(R14))_r$-N(R16)(R17);

or

R1 and R2, together with the nitrogen atom to which they are bonded, form a 4- to 10-membered mono-, bi- or spirocyclic ring which, apart from the nitrogen atom, may include from 0 to 3 additional heteroatoms selected from the group of oxygen, nitrogen and sulfur, where the heterocyclic ring system may additionally be substituted by F, Cl, Br, CF_3, CN, $(C_1$-$C_6)$-alkyl, $(C_3$-$C_8)$-cycloalkyl, O—$(C_1$-$C_8)$-alkyl, $(C_1$-$C_4)$-alkoxy-$(C_1$-$C_4)$-alkyl, hydroxy-$(C_1$-$C_6)$-alkyl, oxo, CO(R18), CON(R19)(R20), hydroxyl, COO(R21), N(R22)$CO(C_1$-$C_6)$-alkyl, N(R23)(R24) or $SO_2(C_1$-$C_6)$-alkyl;

R10, R11 are each independently H, $(C_1$-$C_6)$-alkyl, hydroxy-$(C_1$-$C_2)$-alkyl, F, OH;

R9, R13, R14, R16, R17, R18, R19, R20, R21, R22, R23, R24, are each independently H, $(C_1$-$C_6)$-alkyl;

or

R16 and R17, R23 and R24 form, optionally together with the nitrogen atom to which they are bonded, a 5-6-membered ring which, apart from the nitrogen atom, may also include 0-1 further heteroatom from the group of NH, N—$(C_1$-$C_6)$-alkyl, oxygen and sulfur;

q, r are each independently 0, 1, 2, 3, 4, 5, 6;

R12, R15 are each independently H, OH, F, O—$(C_1$-$C_6)$-alkyl, S—$(C_1$-$C_6)$-alkyl, O-phenyl, CN, COO(R25), N(R26)$CO(C_1$-$C_6)$-alkyl, N(R27)(R28), CON(R29)(R30), $SO_2(C_1$-$C_6)$-alkyl, 3-12-membered mono-, bi- or spirocyclic ring which may contain one to four heteroatoms from the group of N, O and S, and the 3-12-membered ring may contain further substituents such as F, Cl, Br, OH, CF_3, NO_2, CN, OCF_3, oxo, O—$(C_1$-$C_6)$-alkyl, $(C_1$-$C_4)$-alkoxy-$(C_1$-$C_4)$-alkyl, S—$(C_1$-$C_6)$-alkyl, $(C_1$-$C_6)$-alkyl, $(C_2$-$C_6)$-alkenyl, $(C_3$-$C_8)$-cycloalkyl, O—$(C_3$-$C_8)$-cycloalkyl, $(C_3$-$C_8)$-cycloalkenyl, O—$(C_3$-$C_8)$-cycloalkenyl, $(C_2$-$C_6)$-alkynyl, N(R31)(R32), COO(R33), $SO_2(C_1$-$C_6)$-alkyl and COOH;

R25, R26, R27, R28, R29, R30, R31, R32, R33 are each independently H, $(C_1$-$C_8)$-alkyl;

or

R27 and R28, R29 and R30, R31 and R32 each independently form, optionally together with the nitrogen atom to which they are bonded, a 5-6-membered ring which, apart from the nitrogen atom, may also include 0-1 further heteroatom from the group of NH, N—$(C_1$-$C_6)$-alkyl, oxygen and sulfur;

L1 is C(R34)(R35), C(R36)(R37)C(R38)(R39), $(C_3$-$C_6)$-cycloalkyl;

optionally, R1 may be joined to one of the R34, R35, R36, R37, R38 or R39 radicals, so as to form a 5-6-membered ring;

R34, R35, R36, R37, R38, R39 are each independently H, $(C_1$-$C_8)$-alkyl;

R3, R4, R5 are each independently H, F, Cl, Br, I, OH, CF_3, NO_2, CN, OCF_3, O—$(C_1$-$C_8)$-alkyl, S—$(C_1$-$C_8)$-alkyl, O—$(C_1$-$C_4)$-alkoxy-$(C_1$-$C_4)$-alkyl, $(C_1$-$C_6)$-alkyl, CON(R40)(R41), CO(R42);

R40, R41, R42 are each independently H, $(C_1$-$C_8)$-alkyl;

or

R40 and R41 each independently form, optionally together with the nitrogen atom to which they are bonded, a 5-6-membered ring which, apart from the nitrogen atom, may also include 0-1 further heteroatom from the group of NH, N—$(C_1$-$C_8)$-alkyl, oxygen and sulfur;

X is O, C(R43)(R43');

R6, R6', R7, R7', R43, R43' are each independently H, F, $(C_1$-$C_8)$-alkyl, OH, O—$(C_1$-$C_8)$-alkyl;

or

R6 and R6', or R43 and R43' together are optionally oxo;

R8 is H, $(C_1$-$C_8)$-alkyl;

L2 is a bond, C(R44)(R45);

R44, R45 are each independently H, (C_1-C_8)-alkyl;

A is a 5-6-membered aromatic ring which may include up to 2 heteroatoms selected from the group of nitrogen, oxygen and sulfur, and may be substituted by one or more of the substituents H, F, Cl, Br, I, OH, CF_3, NO_2, CN, OCF_3, O—(C_1-C_6)-alkyl, O—(C_1-C_4)-alkoxy-(C_1-C_4)-alkyl, (C_1-C_6)-alkyl, N(R54)(R55), SO_2—CH_3, CON(R56)(R57), N(R58)CO(R59), CO(R60);

in the case that L2=a bond, C(O)NR8 may be joined to an ortho substituent of A via a bridge containing one or two elements from the group of carbon and nitrogen, so as to form a 9- to 10-membered bicyclic ring overall;

R54, R55, R56, R57, R58, R59, R60 are each independently H, (C_1-C_8)-alkyl;

or

R54 and R55, R56 and R57 each independently form, optionally together with the nitrogen atom to which they are bonded, a 5-6-membered ring which, apart from the nitrogen atom, may also include 0-1 further heteroatom from the group of NH, N—(C_1-C_6)-alkyl, oxygen and sulfur;

L3 is a bond or a linker having from 1 to 4 members, where the members are selected from the group consisting of O, S, SO_2, N(R61), CO, C(R62)(R63), C≡C, to give rise to a chemically viable radical, and the linker does not have any O—CO or COO groups;

B is (C_1-C_6)-alkyl, (C_1-C_4)-alkoxy-(C_1-C_4)-alkyl, hydroxy-(C_1-C_6)-alkyl, a 3 to 10-membered mono-, bi- or spirocyclic nonaromatic ring which may include from 0 to 3 heteroatoms selected from the group of oxygen, nitrogen and sulfur, where the ring system may additionally be substituted by one or more of the following substituents: F, CF_3, (C_1-C_6)-alkyl, O—(C_1-C_8)-alkyl, (C_1-C_4)-alkoxy-(C_1-C_4)-alkyl, hydroxy-(C_1-C_4)-alkyl, oxo, CO(R64), hydroxyl;

R61, R62, R63, R64 are each independently H, (C_1-C_8)-alkyl;

where, in the case that X=C(R43)(R43')

L3 is C(R62)(R63)O, and

B is a 4- to 10-membered mono-, bi- or spirocyclic nonaromatic ring which includes from 1 to 3 heteroatoms selected from the group of oxygen, nitrogen and sulfur, where the ring system may additionally be substituted by one or more of the following substituents: F, CF_3, (C_1-C_6)-alkyl, O—(C_1-C_8)-alkyl, (C_1-C_4)-alkoxy-(C_1-C_4)-alkyl, hydroxy-(C_1-C_4)-alkyl, oxo, CO(R64), hydroxyl.

The compounds of the formula I are notable in that they have an improved solubility in aqueous media as compared with structurally similar compounds with MCH-antagonistic action (especially in physiologically relevant buffer systems) coupled with simultaneously high activity. Moreover, preferred inventive compounds are notable for low blockage of the hERG channel. Furthermore, preferred inventive compounds have an improved metabolic stability as compared with prior art compounds.

The alkyl, alkenyl and alkynyl radicals in the substituents R1, R2, R3, R4, R5, R6, R6", R7, R7", R8, R9, R10, R11, R12, R13, R14, R15, R16, R17, R18, R19, R20, R21, R22, R23, R24, R25, R26, R27, R28, R29, R30, R31, R32, R33, R34, R35, R36, R37, R38, R39, R40, R41, R42, R43, R43", R44, R45, R54, R55, R56, R57, R58, R59, R60, R61, R62, R63, R64 may be either straight-chain, branched and/or optionally substituted by substituents such as (C_1-C_4)-alkoxy or halogen. This also applies when the alkyl, alkenyl and alkynyl radicals are part of another group, for example part of an alkoxy group (such as (C_1-C_4)-alkoxy-(C_1-C_4)-alkyl)). Suitable halogens are fluorine, chlorine, bromine and iodine, preferably fluorine, chlorine and bromine, particularly preferably fluorine.

Examples of alkyl groups are: methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl and octyl. Included therein are both the n-isomers of these radicals and branched isomers such as isopropyl, isobutyl, isopentyl, sec-butyl, tert-butyl, neopentyl, 3,3-dimethylbutyl, etc. Unless stated otherwise, the term alkyl additionally also includes alkyl radicals which are unsubstituted or optionally substituted by one or more further radicals, for example by 1, 2, 3 or 4 identical or different radicals such as (C_1-C_4)-alkoxy or halogen. Examples of alkyl groups substituted by halogen are fluorinated alkyl groups such as CF_3, CHF_2, CH_2F, 3-fluoroprop-1-yl, 2,2,1,1-tetrafluoroethyl. It is moreover possible for the additional substituents to appear in any desired position of the alkyl radical. Unless defined otherwise, the alkyl radicals are preferably unsubstituted.

Cycloalkyl means in the context of the present application cycloalkyl and cycloalkylalkyl (alkyl which is in turn substituted by cycloalkyl), where cycloalkyl has at least 3 carbon atoms. Examples of cycloalkyl radicals are: cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl and cyclodecyl. Polycyclic ring systems are also possible where appropriate, such as decalinyl, norbornanyl, bornanyl or adamantanyl. The cycloalkyl radicals may be unsubstituted or optionally substituted by one or more further radicals as listed by way of example above for the alkyl radicals. Unless defined otherwise, the cycloalkyl radicals are preferably unsubstituted.

Examples of alkenyl and alkynyl groups are: vinyl, 1-propenyl, 2-propenyl (allyl), 2-butenyl, 2-methyl-2-propenyl, 3-methyl-2-butenyl, ethynyl, 2-propynyl (propargyl), 2-butynyl or 3-butynyl.

Cycloalkenyl means in the context of the present application cycloalkenyl radicals and cycloalkenylalkyl radicals (alkyl which is substituted by cycloalkenyl), which comprise at least three carbon atoms. Examples of cycloalkenyl are: cyclopentenyl, cyclohexenyl, cycloheptenyl and cyclooctenyl.

The alkenyl radicals and cycloalkenyl radicals may have one to three conjugated or non-conjugated double bonds (i.e. also alkadienyl and alkatrienyl radicals), preferably one double bond in a linear or branched chain. The same applies to the triple bonds for alkynyl radicals. The alkenyl and alkynyl radicals may be unsubstituted or optionally substituted by one or more further radicals as listed by way of example above for the alkyl radicals. Unless defined otherwise, the alkenyl and alkynyl radicals are preferably unsubstituted.

Aryl refers in the present invention to radicals which are derived from monocyclic or bicyclic aromatic compounds comprising no ring heteroatoms. Where aryl refers to systems which are not monocyclic, the saturated form (perhydro form) or the partly unsaturated form (for example the dihydro form or tetrahydro form) is also possible for the second ring when the respective forms are known and stable. The term aryl also includes in the present invention for example bicyclic radicals in which both rings are aromatic and bicyclic radicals in which only one ring is aromatic. Examples of aryl are: phenyl, naphthyl, indanyl, 1,2-dihydronaphthenyl, 1,4-dihydronaphthenyl, indenyl or 1,2,3,4-tetrahydronaphthyl. Unless defined otherwise, the aryl radicals are preferably unsubstituted. Aryl is particularly preferably phenyl or naphthyl.

Heteroaryl radicals mean radicals derived from monocyclic or bicyclic aromatic compounds which comprise ring

heteroatoms, preferably N, O or S. Otherwise, the statements made about aryl radicals apply to heteroaryl radicals.

A "tricycle" means structures having 3 rings which are linked together by more than one bond. Examples of such systems are fused systems with 3 rings and spirocycles with fused-on ring system.

A polycyclic group (bi-, tri- or spirocyclic ring structure) means in the context of the present application a group which is derived from spiranes, fused ring systems or bridged ring systems. The spiranes are notable for two rings having only one carbon atom in common and the ring planes of the two rings being perpendicular to one another. In the fused ring systems, two rings are linked together in such a way that they have two atoms in common. This type of linkage involves an "ortho fusion". Bridged ring systems are ring systems having a bridge of carbon atoms and/or heteroatoms between two nonadjacent atoms of a ring.

A "chemically viable radical" means in the context of the present invention a radical which is stable at room temperature and atmospheric pressure. In the context of the present invention, a "chemically viable radical" in the definition of group A in compounds of the formula I preferably means groups which have no heteroatom-heteroatom bonds between the individual members of the groups.

A "nonaromatic" ring means in the context of the present application preferably a ring which is saturated or partly unsaturated. In this connection, a partly unsaturated ring according to the present application has one or, where appropriate, a plurality of double bonds, but the partly unsaturated ring is not aromatic. The term "nonaromatic" in the context of the present application also includes "nonheteroaromatic" rings.

The compounds of the formula I may have one or more centers of asymmetry. The compounds of the formula I may therefore exist in the form of their racemates, enantiomer-enriched mixtures, pure enantiomers, diastereomers and mixtures of diastereomers. The present invention encompasses all these isomeric forms of the compounds of the formula I. These isomeric forms may be obtained by known methods, even if not expressly described in some cases.

Pharmaceutically acceptable salts are, because their solubility in water is greater than that of the initial or basic compounds, particularly suitable for medical applications. These salts must have a pharmaceutically acceptable anion or cation. Suitable pharmaceutically acceptable acid addition salts of the compounds of the invention are salts of inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, metaphosphoric acid, nitric acid and sulfuric acid, and of organic acids, for example acetic acid, benzenesulfonic acid, benzoic acid, citric acid, ethanesulfonic acid, fumaric acid, gluconic acid, glycolic acid, isethionic acid, lactic acid, lactobionic acid, maleic acid, malic acid, methanesulfonic acid, succinic acid, p-toluenesulfonic acid and tartaric acid. Suitable pharmaceutically acceptable basic salts are ammonium salts, alkali metal salts (such as sodium and potassium salts), alkaline earth metal salts (such as magnesium and calcium salts) and salts of trometamol (2-amino-2-hydroxymethyl-1,3-propanediol), diethanolamine, lysine or ethylenediamine.

Salts with a pharmaceutically unacceptable anion, for example trifluoroacetate, likewise belong within the framework of the invention as useful intermediates for the preparation or purification of pharmaceutically acceptable salts and/or for use in nontherapeutic, for example in vitro, applications.

The term "physiologically functional derivative" used herein refers to any physiologically tolerated derivative of a compound of the formula I of the invention, for example an ester, which on administration to a mammal, for example a human, is able to form (directly or indirectly) a compound of the formula I or an active metabolite thereof.

Physiologically functional derivatives also include prodrugs of the compounds of the invention, as described, for example, in H. Okada et al., Chem. Pharm. Bull. 1994, 42, 57-61. Such prodrugs can be metabolized in vivo to a compound of the invention. These prodrugs may themselves be active or not.

The compounds of the invention may also exist in various polymorphous forms, for example as amorphous and crystalline polymorphous forms. All polymorphous forms of the compounds of the invention belong within the framework of the invention and are a further aspect of the invention.

All references to "compound(s) of formula I" hereinafter refer to compound(s) of the formula I as described above, and their salts, solvates and physiologically functional derivatives as described herein.

If radicals or substituents can occur more than once in the compounds of the formula I, they may each independently be defined as specified and be the same or different.

The symbols in the formula I are preferably each independently defined as follows:

R1, R2

are each independently H, $(C_1$-$C_8)$-alkyl, $(C_1$-$C_4)$-alkoxy-$(C_1$-$C_4)$-alkyl, $(C_3$-$C_8)$-alkenyl, $(C_3$-$C_8)$-alkynyl, CO(R9), $(C(R10)(R11))_q$-R12, $CO(C(R13)(R14))_r$-R15, CO—O$(C_1$-$C_8)$-alkyl, $CO(C(R13)(R14))_rN(R16)(R17)$;

R1 is preferably:

H, $(C_1$-$C_8)$-alkyl, $(C(R10)(R11))_q$-R12, $(C_1$-$C_4)$-alkoxy-$(C_1$-$C_4)$-alkyl, $(C_3$-$C_8)$-alkenyl, $(C_3$-$C_8)$-alkynyl, CO—$(C_1$-$C_8)$-alkyl, CO—O$(C_1$-$C_8)$-alkyl, $CO(C(R13)(R14))_rN(R16)(R17)$;

R2 is preferably:

$(C_1$-$C_8)$-alkyl, $(C(R10)(R11))_q$-R12, $(C_1$-$C_4)$-alkoxy-$(C_1$-$C_4)$-alkyl, $(C_3$-$C_8)$-alkenyl, $(C_3$-$C_8)$-alkynyl;

or

R1 and R2, together with the nitrogen atom to which they bonded, form a 4- to 10-membered mono-, bi- or spirocyclic ring which, apart from the nitrogen atom, may include from 0 to 3 additional heteroatoms selected from the group of oxygen, nitrogen and sulfur, where the heterocyclic ring system may additionally be substituted by F, Cl, Br, CF_3, CN, $(C_1$-$C_6)$-alkyl, $(C_3$-$C_8)$-cycloalkyl, O—$(C_1$-$C_8)$-alkyl, $(C_1$-$C_4)$-alkoxy-$(C_1$-$C_4)$-alkyl, hydroxy-$(C_1$-$C_6)$-alkyl, oxo, CO(R18), CON(R19)(R20), hydroxyl, COO(R21), N(R22)CO$(C_1$-$C_6)$-alkyl, N(R23)(R24) or $SO_2(C_1$-$C_6)$-alkyl;

more preferably, R1, R2 are:

$(C_1$-$C_8)$-alkyl, $(C(R10)(R11))_q$-R12, $(C_1$-$C_4)$-alkoxy-$(C_1$-$C_4)$-alkyl; or R1 and R2, together with the nitrogen atom to which they are bonded, form a 4- to 10-membered mono-, bi- or spirocyclic ring which, apart from the nitrogen, may include from 0 to 2 additional heteroatoms selected from the group of oxygen, nitrogen and sulfur, where the heterocyclic ring system may additionally be substituted by F, Cl, Br, CF_3, $(C_1$-$C_6)$-alkyl, O—$(C_1$-$C_8)$-alkyl, $(C_3$-$C_8)$-cycloalkyl, $(C_1$-$C_4)$-alkoxy-$(C_1$-$C_4)$-alkyl, hydroxy-$(C_1$-$C_6)$-alkyl, oxo, CO(R18), hydroxyl, N(R22)CO$(C_1$-$C_6)$-alkyl, or SO_2 $(C_1$-$C_6)$-alkyl;

most preferably, R1 and R2, together with the nitrogen atom to which they are bonded, form a 4- to 10-membered mono-, bi- or spirocyclic ring which, apart from the nitrogen atom, may include from 0 to 2 additional

heteroatoms selected from the group of oxygen, nitrogen and sulfur, where the heterocyclic ring system may additionally be substituted by F, Cl, Br, CF_3, $(C_1$-$C_6)$-alkyl, O—$(C_1$-$C_8)$-alkyl, $(C_3$-$C_8)$-cycloalkyl, $(C_1$-$C_4)$-alkoxy-$(C_1$-$C_4)$-alkyl, hydroxy-$(C_1$-$C_6)$-alkyl, oxo, CO(R18), hydroxyl, N(R22)CO$(C_1$-$C_6)$-alkyl, or SO_2 $(C_1$-$C_6)$-alkyl;

R10, R11

are each independently H, $(C_1$-$C_6)$-alkyl, hydroxy-$(C_1$-$C_2)$-alkyl, F, OH;

R9, R13, R14, R16, R17, R18, R19, R20, R21, R22, R23, R24,

are each independently H, $(C_1$-$C_6)$-alkyl;

or

R16 and R17, R23 and R24 form, optionally together with the nitrogen atom to which they are bonded, a 5-6-membered ring which, apart from the nitrogen atom, may also include 0-1 further heteroatom from the group of NH, N—$(C_1$-$C_6)$-alkyl, oxygen and sulfur;

q, r are each independently 0, 1, 2, 3, 4, 5, 6; preferably 0, 1, 2, 3, 4;

R12, R15 are each independently H, OH, F, O—$(C_1$-$C_6)$-alkyl, S—$(C_1$-$C_6)$-alkyl, O-phenyl, CN, COO(R25), N(R26)CO$(C_1$-$C_6)$-alkyl, N(R27)(R28), CON(R29)(R30), $SO_2(C_1$-$C_6)$-alkyl, 3-12-membered mono-, bi- or spirocyclic ring which may contain one to four heteroatoms from the group of N, O and S, and the 3-12-membered ring may contain further substituents such as F, Cl, Br, OH, CF_3, NO_2, CN, OCF_3, oxo, O—$(C_1$-$C_6)$-alkyl, $(C_1$-$C_4)$-alkoxy-$(C_1$-$C_4)$-alkyl, S—$(C_1$-$C_6)$-alkyl, $(C_1$-$C_6)$-alkyl, $(C_2$-$C_6)$-alkenyl, $(C_3$-$C_8)$-cycloalkyl, O—$(C_3$-$C_8)$-cycloalkyl, $(C_3$-$C_8)$-cycloalkenyl, O—$(C_3$-$C_8)$-cycloalkenyl, $(C_2$-$C_6)$-alkynyl, N(R31)(R32), COO(R33), $SO_2(C_1$-$C_6)$-alkyl and COOH;

preferably H, OH, F, O—$(C_1$-$C_6)$-alkyl, N(R26)CO$(C_1$-$C_6)$-alkyl, $SO_2(C_1$-$C_6)$-alkyl, 3-12 membered mono-, bi- or spirocyclic ring which may contain one to three heteroatoms from the group of N, O and S, and the 3-12-membered ring may contain further substituents such as F, Cl, Br, OH, CF_3, NO_2, CN, OCF_3, oxo, O—$(C_1$-$C_6)$-alkyl, $(C_1$-$C_4)$-alkoxy-$(C_1$-$C_4)$-alkyl, $(C_1$-$C_6)$-alkyl, $(C_2$-$C_6)$-alkenyl, $(C_2$-$C_6)$-alkynyl, N(R31)(R32) and $SO_2(C_1$-$C_6)$-alkyl;

R25, R26, R27, R28, R29, R30, R31, R32, R33 are each independently H, $(C_1$-$C_8)$-alkyl;

or

R27 and R28, R29 and R30, R31 and R32 each independently form, optionally together with the nitrogen atom to which they are bonded, a 5-6-membered ring which, apart from the nitrogen atom, may also include 0-1 further heteroatom from the group of NH, N—$(C_1$-$C_6)$-alkyl, oxygen and sulfur;

L1 is C(R34)(R35), C(R36)(R37)C(R38)(R39), $(C_3$-$C_6)$-cycloalkyl;

preferably C(R34)(R35);

optionally, R1 may be joined to one of the R34, R35, R36, R37, R38 or R39 radicals, so as to form a 5-6-membered ring;

R34, R35, R36, R37, R38, R39 are each independently H, $(C_1$-$C_8)$-alkyl;

R3, R4, R5 are each independently H, F, Cl, Br, I, OH, CF_3, NO_2, CN, OCF_3, O—$(C_1$-$C_6)$-alkyl, S—$(C_1$-$C_6)$-alkyl, O—$(C_1$-$C_4)$-alkoxy-$(C_1$-$C_4)$-alkyl, $(C_1$-$C_6)$-alkyl, CON(R40)(R41), CO(R42);

preferably each independently H, F, Cl, Br, CF_3, CN, OCF_3, O—$(C_1$-$C_6)$-alkyl, $(C_1$-$C_4)$-alkoxy-$(C_1$-$C_4)$-alkyl, $(C_1$-$C_6)$-alkyl, CO$(C_1$-$C_6)$-alkyl;

more preferably each independently H, F, Cl, Br, CF_3, CN, OCF_3, O—$(C_1$-$C_6)$-alkyl, $(C_1$-$C_4)$-alkoxy-$(C_1$-$C_4)$-alkyl, $(C_1$-$C_6)$-alkyl;

even more preferably each independently H, F, Cl, O—$(C_1$-$C_6)$-alkyl, $(C_1$-$C_6)$-alkyl;

very especially preferably H;

where preferably at least two or all R3, R4 and R5 radicals are H;

R40, R41, R42 are each independently H, $(C_1$-$C_8)$-alkyl;

or

R40 and R41 each independently form, optionally together with the nitrogen atom to which they are bonded, a 5-6-membered ring which, apart from the nitrogen atom, may also include 0-1 further heteroatom from the group of NH, N—$(C_1$-$C_6)$-alkyl, oxygen and sulfur;

X is O, C(R43)(R43');

R6, R6', R7, R7', R43, R43' are each independently H, F, $(C_1$-$C_8)$-alkyl, OH, O—$(C_1$-$C_6)$-alkyl;

preferably H;

or

R6 and R6', or R43 and R43' together are optionally oxo;

R8 is H, $(C_1$-$C_8)$-alkyl;

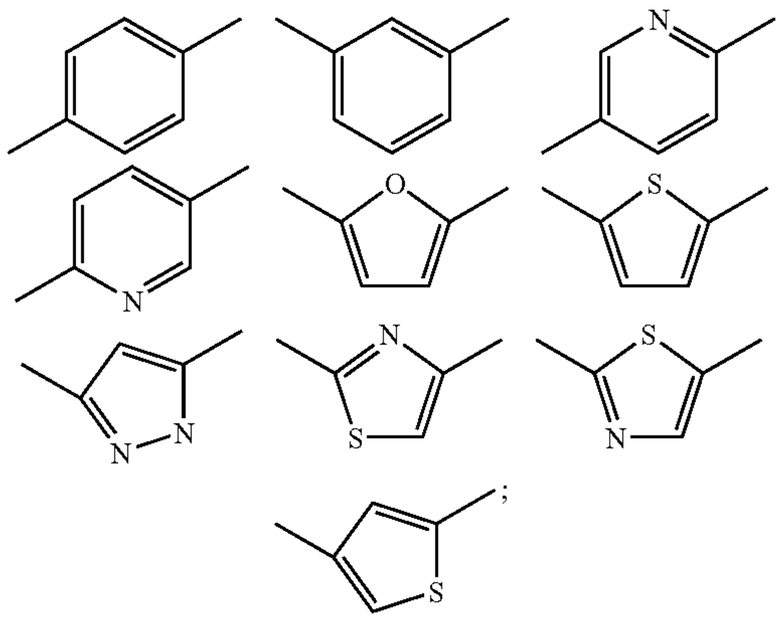
L2 is a bond, C(R44)(R45);

preferably a bond;

R44, R45 are each independently H, $(C_1$-$C_8)$-alkyl;

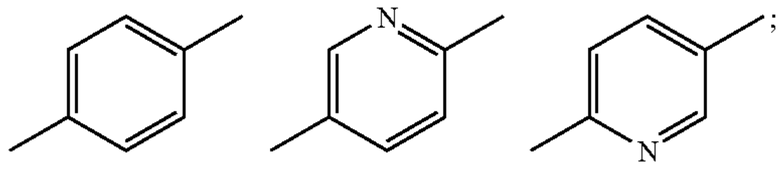
A is a 5-6-membered aromatic ring which may include up to 2 heteroatoms selected from the group of nitrogen, oxygen and sulfur, and may be substituted by one or more of the substituents H, F, Cl, Br, I, OH, CF_3, NO_2, CN, OCF_3, O—$(C_1$-$C_6)$-alkyl, O—$(C_1$-$C_4)$-alkoxy-$(C_1$-$C_4)$-alkyl, $(C_1$-$C_6)$-alkyl, N(R54)(R55), SO_2—CH_3, CON(R56)(R57), N(R58)CO(R59), CO(R60); preferably H, F, Cl, Br, I, OH, CF_3, NO_2, CN, OCF_3, O—$(C_1$-$C_6)$-alkyl, $(C_1$-$C_4)$-alkoxy-$(C_1$-$C_4)$-alkyl, $(C_1$-$C_6)$-alkyl; more preferably H, F, Cl, Br, CF_3, CN, OCF_3, O—$(C_1$-$C_6)$-alkyl, $(C_1$-$C_4)$-alkoxy-$(C_1$-$C_4)$-alkyl, $(C_1$-$C_6)$-alkyl; even more preferably H, F, Cl, O—$(C_1$-$C_6)$-alkyl, $(C_1$-$C_6)$-alkyl; very especially preferably H;

the 5-6-membered aromatic ring is preferably selected from the group consisting of



;

more preferably



;

in the case that L2=a bond, C(O)NR8 may be joined to an ortho substituent of A via a bridge containing one or two elements from the group of carbon and nitrogen, so as to form a 9- to 10-membered bicyclic ring overall;

the bridge preferably contains two carbon elements, so as to form an isoquinolinone or a dihydroisoquinolinone overall;

R54, R55, R56, R57, R58, R59, R60 are each independently H, (C_1-C_8)-alkyl;

or

R54 and R55, R56 and R57 each independently form, optionally together with the nitrogen atom to which they are bonded, a 5-6-membered ring which, apart from the nitrogen atom, may also include 0-1 further heteroatom from the group of NH, N—(C_1-C_6)-alkyl, oxygen and sulfur;

L3 is a bond or a linker having from 1 to 4 members, where the members are selected from the group consisting of O, S, SO_2, N(R61), CO, C(R62)(R63), C≡C, to give rise to a chemically viable radical, and the linker does not have any O—CO or COO groups;

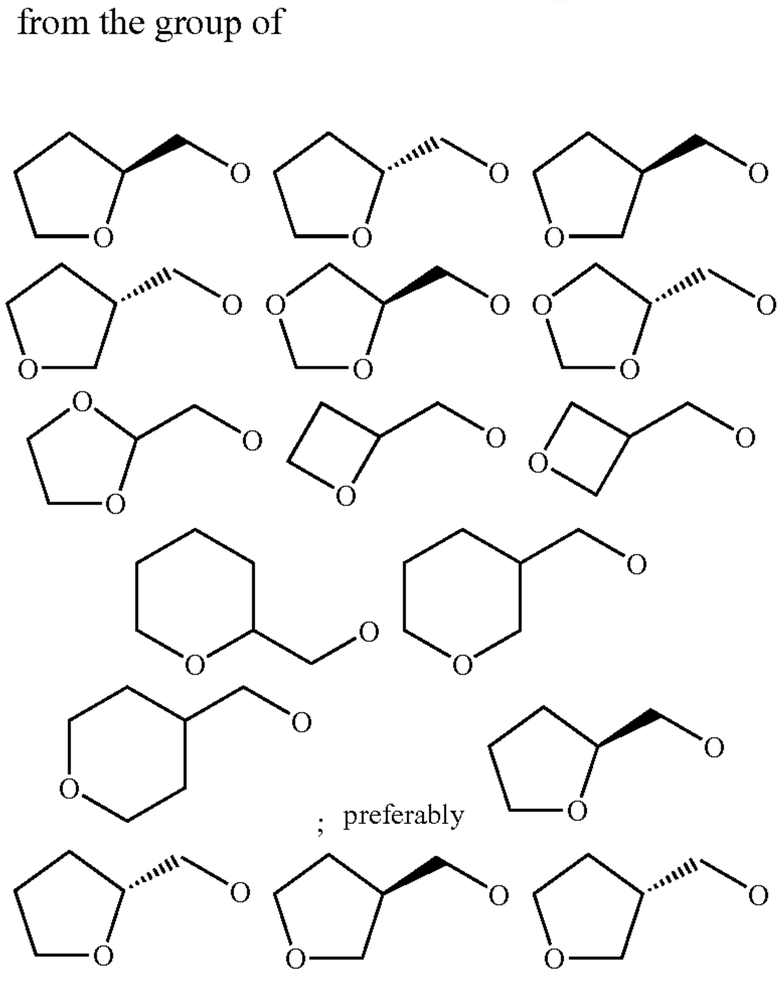
preferably a bond or a linker having from 1 to 4 members, where the members are selected from the group consisting of O, N(R61), CO, C(R62)(R63), to give rise to a chemically viable radical, and the linker does not have any O—CO or COO groups;

more preferably a bond, O, C(R62)(R63)O;

B is (C_1-C_6)-alkyl, (C_1-C_4)-alkoxy-(C_1-C_4)-alkyl, hydroxy-(C_1-C_6)alkyl, a 3- to 10-membered mono-, bi- or spirocyclic nonaromatic ring which includes from 0 to 3 heteroatoms selected from the group of oxygen, nitrogen and sulfur, where the ring system may additionally be substituted by one or more of the following substituents: F, CF_3, (C_1-C_6)-alkyl, O—(C_1-C_8)-alkyl, (C_1-C_4)-alkoxy-(C_1-C_4)-alkyl, hydroxy-(C_1-C_4)-alkyl, oxo, CO(R64), hydroxyl;

preferably a 4- to 6-membered nonaromatic ring which includes from 1 to 2 oxygen atoms, where the ring system may additionally be substituted by one or more of the following substituents: F, (C_1-C_6)-alkyl, O—(C_1-C_8)-alkyl, (C_1-C_4)-alkoxy-(C_1-C_4)-alkyl, oxo, hydroxyl, preferably (C_1-C_6)-alkyl or hydroxyl;

the combined element B-L3 is more preferably selected from the group of



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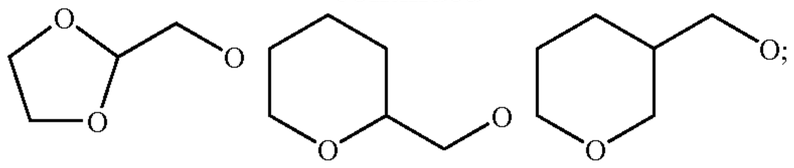
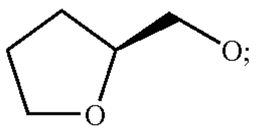


more preferably



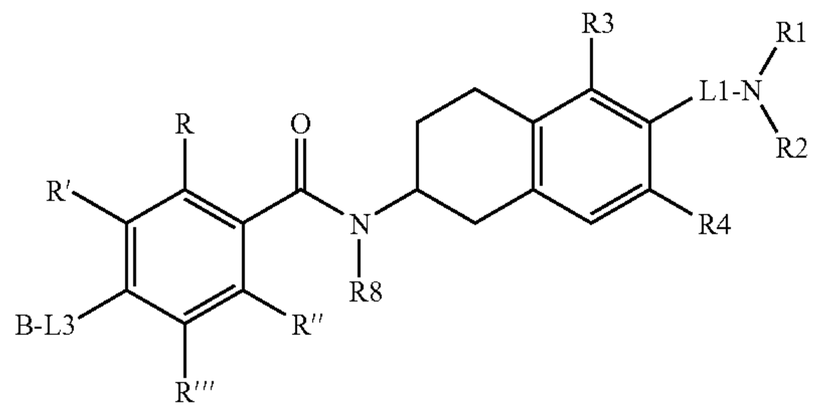
R61, R62, R63, R64 are each independently H, (C_1-C_8)-alkyl;

where, in the case that X═C(R43)(R43')

L3 is C(R62)(R63)O, and

B is a 4- to 10-membered mono-, bi- or spirocyclic nonaromatic ring which includes from 1 to 3 heteroatoms selected from the group of oxygen, nitrogen and sulfur, where the ring system may additionally be substituted by one or more of the following substituents: F, CF_3, (C_1-C_6)-alkyl, O—(C_1-C_8)-alkyl, (C_1-C_4)-alkoxy-(C_1-C_4)-alkyl, hydroxy-(C_1-C_4)-alkyl, oxo, CO(R64), hydroxyl.

A particular aspect of the invention is that of compounds of the formula II



II

in which the variables R1, R2, L1, R3, R4 and R8 are each as defined above and

R, R', R'', R'''

are each independently H, F, Cl, Br, I, OH, CF_3, NO_2, CN, OCF_3, O—(C_1-C_6)-alkyl, O—(C_1-C_4)-alkoxy-(C_1-C_4)-alkyl, (C_1-C_6)-alkyl, N(R54)(R55), SO_2—CH_3, CON(R56)(R57), N(R58)CO(R59), CO(R60);

preferably each independently H, F, Cl, Br, I, OH, CF_3, NO_2, CN, OCF_3, O —(C_1-C_6)-alkyl, (C_1-C_4)-alkoxy-(C_1-C_4)-alkyl, (C_1-C_6)-alkyl;

more preferably each independently H, F, Cl, Br, CF_3, CN, OCF_3, O—(C_1-C_6)-alkyl, (C_1-C_4)-alkoxy-(C_1-C_4)-alkyl, (C_1-C_6)-alkyl;

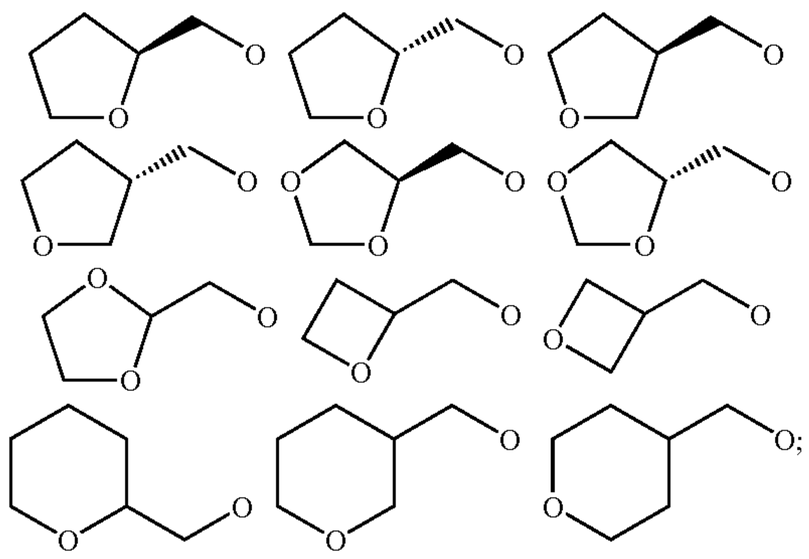
even more preferably each independently H, F, Cl, O—(C_1-C_6)-alkyl, (C_1-C_6)-alkyl;

very especially preferably H;

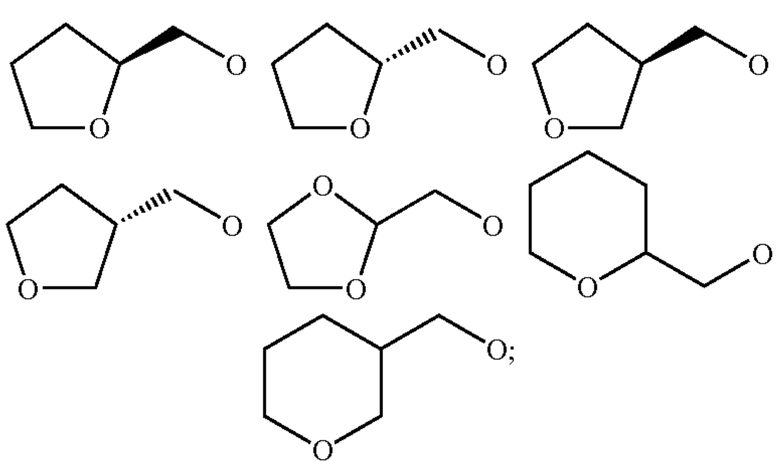
L3 is CH_2O;

B is a 4- to 6-membered nonaromatic ring which includes from 1 to 2 oxygen atoms, where the ring system may additionally be substituted by one or more of the following substituents: F, (C_1-C_6)-alkyl, O—(C_1-C_8)-alkyl, (C_1-C_4)-alkoxy-(C_1-C_4)-alkyl, oxo, hydroxyl, preferably (C_1-C_6)-alkyl or hydroxyl;

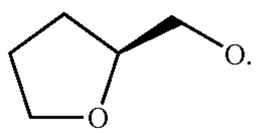
the combined element B-L3 is preferably selected from the group of



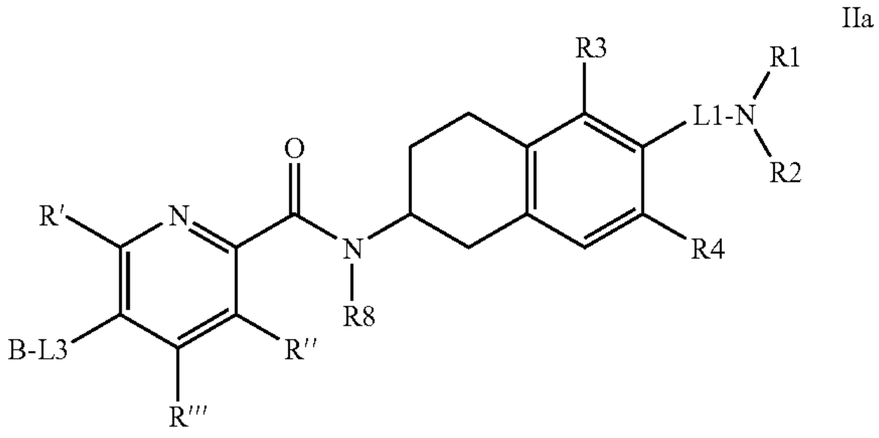
more preferably



especially preferably



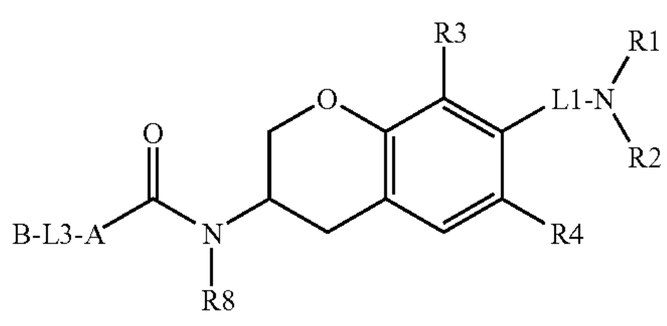
A further particular aspect of the invention is that of compounds of the formula IIa



IIa

in which the variables R1, R2, L1, R3, R4, R8, R', R", R", L3 and B are each as defined above.

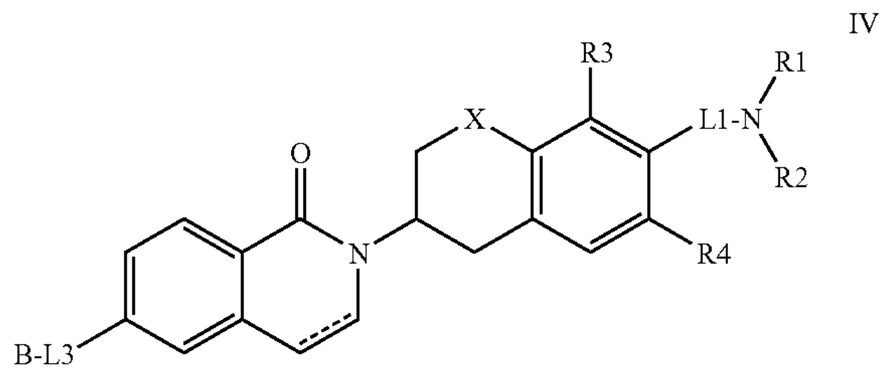
In a further particular aspect, the invention relates to compounds of the formula III



III

in which R1, R2, R3, R4, R8, A, L1, L3 and B are each as defined for formula I.

In another particular aspect, the invention relates to compounds of the formula IV



IV

in which R1, R2, R3, R4, X, L1, L3 and B are each as defined for formula I. The broken line indicates an optional double bond, such that both dihydroisoquinolinones and isoquinolinones are encompassed by the formula IV.

The inventive compounds of the general formula I can be prepared analogously to processes known to those skilled in the art. Suitable processes for preparing the inventive compounds of the general formula I are mentioned below by way of example (see especially methods A, B, C, D, E, F, G, H, I, J, K, L, M, N, O, P and schemes 1 to 3).

Preferred embodiments of the steps mentioned, just like the preparation of the starting substances used in the steps, are known to those skilled in the art and are mentioned by way of example in the schemes and methods mentioned, and also examples.

This invention further relates to the use of compounds of the formula I and pharmaceutical compositions thereof as MCH receptor ligands. The inventive MCH receptor ligands are suitable especially as modulators of the activity of MCH R1

The role of MCH in regulating the energy balance has now been well documented (Qu, D. et al. Nature 1996, 380, 243-7; Shimada, M. et al. Nature 1998, 396, 670-4; Chen, Y et al. Endocrinology 2002, 143, 2469-77; Endocrinology 2003, 144, 4831-40; Reviews: G. Hervieu, Expert Opin. Ther. Targets 2003, 7, 495-511; Shi, Y., Peptides 2004, 25, 1605-11; Pissios, P. et al., Endocrine Rev. 2006, 27, 606-20; Luthin, D. R., Life Sci. 2007, 81, 423-440).

There are also indications that MCH antagonists can have a beneficial influence on centrally related disorders such as, for example, anxiety neuroses and depressions (Borowsky, B. et al. Nature Medicine 2002, 8, 825-30; Reviews: G. Hervieu, Expert Opin. Ther. Targets 2003, 7, 495-511; Chaki, S. et al., Drug Dev. Res. 2005, 65, 278-290; Dyck, B., Drug Dev. Res. 2005, 65, 291-300; Shimazaki, T., CNS Drugs 2006, 20, 801-11; Drugs Fut. 2007, 32, 809-822).

Compounds of this type are particularly suitable for the treatment and/or prevention of

1. Obesity
2. Diabetes mellitus, especially type 2 diabetes, including the prevention of the sequelae associated therewith.

   Particular aspects in this connection are

   hyperglycemia,

   improvement in insulin resistance,

   improvement in glucose tolerance,

   protection of the pancreatic β cells

   prevention of macro- and microvascular disorders
3. Dyslipidemias and the sequelae thereof such as, for example, atherosclerosis, coronary heart disease, cerebrovascular disorders etc., especially (but not restricted to)

those which are characterized by one or more of the following factors:

high plasma triglyceride concentrations, high postprandial plasma triglyceride concentrations

low HDL cholesterol concentration

4. Fatty liver, especially nonalcoholic fatty liver and variants thereof,

steatosis

steatohepatitis

cirrhosis.

5. Various other conditions which may be associated with the metabolic syndrome, such as:

thromboses, hypercoagulable and prothrombotic stages (arterial and venous)

high blood pressure

heart failure such as, for example (but not restricted thereto), following myocardial infarction, hypertensive heart disease or cardiomyopathy

6. Psychiatric indications such as

depressions

anxiety states

disturbances of the circadian rhythm

affection disorders

schizophrenia

addictive disorders

7. Sleep disorders such as

sleep apnea

narcolepsy

8. Inflammation disorders such as

inflammatory bowel disease

Crohn's disease

Formulations

The amount of a compound of formula I necessary to achieve the desired biological effect depends on a number of factors, for example the specific compound chosen, the intended use, the mode of administration and the clinical condition of the patient. The daily dose is generally in the range from 0.001 mg to 100 mg (typically from 0.01 mg to 50 mg) per day and per kilogram of body weight, for example 0.1-10 mg/kg/day. An intravenous dose may be, for example, in the range from 0.001 mg to 1.0 mg/kg, which can suitably be administered as infusion of 10 ng to 100 ng per kilogram and per minute. Suitable infusion solutions for these purposes may contain, for example, from 0.1 ng to 10 mg, typically from 1 ng to 10 mg, per milliliter. Single doses may contain, for example, from 1 mg to 10 g of the active ingredient. Thus, ampoules for injections may contain, for example, from 1 mg to 100 mg, and single-dose formulations which can be administered orally, such as, for example, tablets or capsules, may contain, for example, from 0.05 to 1000 mg, typically from 0.5 to 600 mg. For the therapy of the abovementioned conditions, the compounds of formula I may be used as the compound itself, but they are preferably in the form of a pharmaceutical composition with an acceptable carrier. The carrier must, of course, be acceptable in the sense that it is compatible with the other ingredients of the composition and is not harmful for the patient's health. The carrier may be a solid or a liquid or both and is preferably formulated with the compound as a single dose, for example as a tablet, which may contain from 0.05% to 95% by weight of the active ingredient. Other pharmaceutically active substances may likewise be present, including other compounds of formula I. The pharmaceutical compositions of the invention can be produced by one of the known pharmaceutical methods, which essentially consist of mixing the ingredients with pharmacologically acceptable carriers and/or excipients.

Pharmaceutical compositions of the invention are those suitable for oral, rectal, topical, peroral (for example sublingual) and parenteral (for example subcutaneous, intramuscular, intradermal or intravenous) administration, although the most suitable mode of administration depends in each individual case on the nature and severity of the condition to be treated and on the nature of the compound of formula I used in each case. Coated formulations and coated slow-release formulations also belong within the framework of the invention. Preference is given to acid- and gastric juice-resistant formulations. Suitable coatings resistant to gastric juice comprise cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropylmethylcellulose phthalate and anionic polymers of methacrylic acid and methyl methacrylate.

Suitable pharmaceutical preparations for oral administration may be in the form of separate units such as, for example, capsules, cachets, suckable tablets or tablets, each of which contains a defined amount of at least one compound of formula I; as powders or granules; as solution or suspension in an aqueous or nonaqueous liquid; or as an oil-in-water or water-in-oil emulsion. These compositions may, as already mentioned, be prepared by any suitable pharmaceutical method which includes a step in which the active ingredient and the carrier (which may consist of one or more additional ingredients) are brought into contact. The compositions are generally produced by uniform and homogeneous mixing of the active ingredient with a liquid and/or finely divided solid carrier, after which the product is shaped if necessary. Thus, for example, a tablet can be produced by compressing or molding a powder or granules of the compound, where appropriate with one or more additional ingredients. Compressed tablets can be produced by tableting the compound in free-flowing form such as, for example, a powder or granules, where appropriate mixed with a binder, glidant, inert diluent and/or one (or more) surface-active/dispersing agent(s) in a suitable machine. Molded tablets can be produced by molding the compound, which is in powder form and is moistened with an inert liquid diluent, in a suitable machine.

Pharmaceutical compositions which are suitable for peroral (sublingual) administration comprise suckable tablets which contain at least one compound of formula I with a flavoring, normally sucrose and gum arabic or tragacanth, and pastilles which comprise the compound in an inert base such as gelatin and glycerol or sucrose and gum arabic.

Pharmaceutical compositions suitable for parenteral administration comprise preferably sterile aqueous preparations of at least one compound of formula I, which are preferably isotonic with the blood of the intended recipient. These preparations are preferably administered intravenously, although administration may also take place by subcutaneous, intramuscular or intradermal injection. These preparations can preferably be produced by mixing the compound with water and making the resulting solution sterile and isotonic with blood. Injectable compositions of the invention generally contain from 0.1 to 5% by weight of the active compound.

Pharmaceutical compositions suitable for rectal administration are preferably in the form of single-dose suppositories. These can be produced by mixing at least one compound of the formula I with one or more conventional solid carriers, for example cocoa butter, and shaping the resulting mixture.

Pharmaceutical compositions suitable for topical use on the skin are preferably in the form of ointment, cream, lotion, paste, spray, aerosol or oil. Carriers which can be used are petrolatum, lanolin, polyethylene glycols, alcohols and combinations of two or more of these substances. The active

ingredient is generally present in a concentration of from 0.1 to 15% by weight of the composition, for example from 0.5 to 2%.

Transdermal administration is also possible. Pharmaceutical compositions suitable for transdermal uses can be in the form of single patches which are suitable for long-term close contact with the patient's epidermis. Such patches suitably contain the active ingredient in an aqueous solution which is buffered where appropriate, dissolved and/or dispersed in an adhesive or dispersed in a polymer. A suitable active ingredient concentration is about 1% to 35%, preferably about 3% to 15%. A particular possibility is for the active ingredient to be released by electrotransport or iontophoresis as described, for example, in Pharmaceutical Research, 2(6): 318 (1986).

The compounds of the formula I are distinguished by beneficial effects on lipid metabolism, and they are particularly suitable for weight reduction and for maintaining a reduced weight after weight reduction has taken place in mammals and as anorectic agents. The compounds are distinguished as selective MCH1R antagonists by their low toxicity, the small effect on metabolizing enzymes and their few side effects. In particular, preferred compounds of the invention are notable for low blockade of the hERG channel. In addition, preferred compounds of the formula I are noticeably soluble in aqueous systems and thus particularly suitable for pharmaceutical development. The pharmacological effect is moreover achieved in in vivo test models after oral administration from well-tolerated vehicles.

The compounds can be employed alone or in combination with other weight-reducing or anorectic active ingredients. Further anorectic active ingredients of this type are mentioned, for example, in the Rote Liste, chapter 01 under weight-reducing agents/appetite suppressants, and may also include active ingredients which increase the energy turnover of the organism and thus lead to weight reduction or else those which influence the general metabolism of the organism in such a way that an increased calorie intake does not lead to an enlargement of the fat depots and a normal calorie intake leads to a reduction of the fat depots of the organism. The compounds are suitable for the prophylaxis and, in particular, for the treatment of excessive weight or obesity. The compounds are further suitable for the prophylaxis and, in particular, for the treatment of type II diabetes, of arteriosclerosis and for normalizing lipid metabolism and for the treatment of high blood pressure.

Combinations with Other Medicaments

The compounds of the invention can be administered alone or in combination with one or more further pharmacologically active substances which have, for example, beneficial effects on metabolic disturbances or disorders frequently associated therewith. Examples of such medicaments are

1. medicaments which lower blood glucose, antidiabetics,
2. active ingredients for the treatment of dyslipidemias,
3. antiatherosclerotic medicaments,
4. antiobesity agents,
5. antiinflammatory active ingredients
6. active ingredients for the treatment of malignant tumors
7. antithrombotic active ingredients
8. active ingredients for the treatment of high blood pressure
9. active ingredients for the treatment of heart failure and
10. active ingredients for the treatment and/or prevention of complications caused by diabetes or associated with diabetes.

They can be combined with the compounds of the invention of the formula I in particular for a synergistic improvement in action. The active ingredient combination can be administered either by separate administration of the active ingredients to the patient or in the form of combination products in which a plurality of active ingredients are present in one pharmaceutical preparation.

Further suitable active ingredients for the combination preparations are:

All antidiabetics which are mentioned in the Rote Liste 2007, chapter 12; all weight-reducing agents/appetite suppressants which are mentioned in the Rote Liste 2007, chapter 1; all diuretics which are mentioned in the Rote Liste 2007, chapter 36; all lipid-lowering agents which are mentioned in the Rote Liste 2007, chapter 58. They can be combined with the compound of the invention of the formula I in particular for a synergistic improvement in action. The active ingredient combination can be administered either by separate administration of the active ingredients to the patient or in the form of combination products in which a plurality of active ingredients are present in one pharmaceutical preparation. If the active ingredients are administered separately, this can be done simultaneously or successively. Most of the active ingredients mentioned hereinafter are disclosed in the USP Dictionary of USAN and International Drug Names, US Pharmacopeia, Rockville 2006.

Antidiabetics include insulin and insulin derivatives, for example LANTUS® (insulin glargine, also see www.lantus.com) or HMR 1964 or LEVEMIR® (insulin detemir), HUMALOG® (Insulin Lispro), HUMULIN®, VIAJECT™, SULIXEN® or those as described in WO2005005477 (Novo Nordisk), fast-acting insulins (see U.S. Pat. No. 6,221,633), inhalable insulins, for example EXUBERA®, NASULIN™, or oral insulins, for example IN-105 (Nobex) or ORALLYN™ (Generex Biotechnology), or TECHNOSPHERE® Insulin (MannKind) or COBALAMIN™ oral insulin, or insulins as described in WO2007128815, WO2007128817, WO2008034881, WO2008049711, or insulins which can be administered transdermally; GLP-1 derivatives and GLP-1 agonists, for example exenatide or specific formulations thereof, as described, for example, in WO2008061355, liraglutide, taspoglutide or those which have been disclosed in WO 98/08871, WO2005027978, WO2006037811, WO2006037810 by Novo Nordisk A/S, in WO 01/04156 by Zealand or in WO 00/34331 by Beaufour-Ipsen, pramlintide acetate (Symlin; Amylin Pharmaceuticals), AVE-0010, BIM-51077 (R-1583, ITM-077), PC-DAC:Exendin-4 (an exendin-4 analog which is bonded covalently to recombinant human albumin), CVX-73, CVX-98 and CVx-96 (GLP-1 analog which is bonded covalently to a monoclonal antibody which has specific binding sites for the GLP-1 peptide), CNTO-736 (a GLP-1 analog which is bonded to a domain which includes the Fc portion of an antibody), PGC-GLP-1 (GLP-1 bonded to a nanocarrier), agonists, as described, for example, in D. Chen et al., Proc. Natl. Acad. Sci. USA 104 (2007) 943, those as described in WO2006124529, WO2007124461, peptides, for example obinepitide (TM-30338), amylin receptor agonists, as described, for example, in WO2007104789, analogs of the human GLP-1, as described in WO2007120899, WO2008022015, WO2008056726, and orally active hypoglycemic ingredients.

Antidiabetics also include agonists of the glucose-dependent insulinotropic polypeptide (GIP) receptor, as described, for example, in WO2006121860.

Antidiabetics also include the glucose-dependent insulinotropic polypeptide (GIP), and also analogous compounds, as described, for example, in WO2008021560.

Antidiabetics also include analogs and derivatives of fibroblast growth factor 21 (FGF-21).

The orally active hypoglycemic ingredients preferably include
sulfonylureas,
biguanidines,
meglitinides,
oxadiazolidfinediones,
thiazolidinediones,
PPAR and RXR modulators,
glucosidase inhibitors,
inhibitors of glycogen phosphorylase,
glucagon receptor antagonists,
glucokinase activators,
inhibitors of fructose 1,6-bisphosphatase
modulators of glucose transporter 4 (GLUT4),
inhibitors of glutamine-fructose-6-phosphate amidotransferase (GFAT),
GLP-1 agonists,
potassium channel openers, for example pinacidil, cromakalim, diazoxide, or those as described in R. D. Carr et al., Diabetes 52, 2003, 2513.2518, in J. B. Hansen et al, Current Medicinal Chemistry 11, 2004, 1595-1615, in T. M. Tagmose et al., J. Med. Chem. 47, 2004, 3202-3211 or in M. J. Goghlan et al., J. Med. Chem. 44, 2001, 1627-1653, or those which have been disclosed in WO 97/26265 and WO 99/03861 by Novo Nordisk A/S,
active ingredients which act on the ATP-dependent potassium channel of the beta cells,
inhibitors of dipeptidylpeptidase IV (DPP-IV),
insulin sensitizers,
inhibitors of liver enzymes involved in stimulating gluconeogenesis and/or glycogenolysis,
modulators of glucose uptake, of glucose transport and of glucose reabsorption,
modulators of sodium-dependent glucose transporter 1 or 2 (SGLT1, SGLT2),
inhibitors of 11-beta-hydroxysteroid dehydrogenase-1 (11β-HSD1),
inhibitors of protein tyrosine phosphatase 1B (PTP-1B),
nicotinic acid receptor agonists,
inhibitors of hormone-sensitive or endothelial lipases,
inhibitors of acetyl-CoA carboxylase (ACC1 and/or ACC2) or
inhibitors of GSK-3 beta.

Also included are compounds which modify the metabolism, such as active antihyperlipidemic ingredients and active antilipidemic ingredients,
HMGCoA reductase inhibitors,
farnesoid X receptor (FXR) modulators,
fibrates,
cholesterol reabsorption inhibitors,
CETP inhibitors,
bile acid reabsorption inhibitors,
MTP inhibitors,
agonists of estrogen receptor gamma (ERRγ agonists),
sigma-1 receptor antagonists,
antagonists of the somatostatin 5 receptor (SST5 receptor);
compounds which reduce food intake, and
compounds which increase thermogenesis.

In one embodiment of the invention, the compound of the formula I is administered in combination with insulin.

In one embodiment, the compound of the formula I is administered in combination with an active ingredient which acts on the ATP-dependent potassium channel of the beta cells, for example sulfonylureas, for example tolbutamide, glibenclamide, glipizide, gliclazide or glimepiride.

In one embodiment, the compound of the formula I is administered in combination with a tablet which comprises both glimepiride, which is released rapidly, and metformin, which is released over a longer period (as described, for example, in US2007264331, WO2008050987).

In one embodiment, the compound of the formula I is administered in combination with a biguanide, for example metformin.

In another embodiment, the compound of the formula I is administered in combination with a meglitinide, for example repaglinide, nateglinid or mitiglinide.

In a further embodiment, the compound of the formula I is administered with a combination of mitiglinide with a glitazone, e.g. pioglitazone hydrochloride.

In a further embodiment, the compound of the formula I is administered with a combination of mitiglinide with an alpha-glucosidase inhibitor.

In a further embodiment, the compound of the formula I is administered in combination with antidiabetic compounds, as described in WO2007095462, WO2007101060, WO2007105650.

In a further embodiment, the compound of the formula I is administered in combination with antihypoglycemic compounds, as described in WO2007137008.

In one embodiment, the compound of the formula I is administered in combination with a thiazolidinedione, for example troglitazone, ciglitazone, pioglitazone, rosiglitazone or the compounds disclosed in WO 97/41097 by Dr. Reddy's Research Foundation, especially 5-[[4-[(3,4-dihydro-3-methyl-4-oxo-2-quinazolinyl-methoxy]phenyl]methyl]-2,4-thiazolidinedione.

In one embodiment of the invention, the compound of the formula I is administered in combination with a PPAR gamma agonist, for example rosiglitazone, pioglitazone, JTT-501, GI 262570, R-483, CS-011 (rivoglitazone), DRL-17564, DRF-2593 (Balaglitazon), INT-131, T-2384, or those as described in WO2005086904, WO2007060992, WO2007100027, WO2007103252, WO2007122970, WO2007138485, WO2008006319, WO2008006969, WO2008010238, WO2008017398, WO2008028188.

In one embodiment of the invention, the compound of the formula I is administered in combination with Competact™, a solid combination of pioglitazone hydrochloride with metformin hydrochloride.

In one embodiment of the invention, the compound of the formula I is administered in combination with Tandemact™, a solid combination of pioglitazone with glimepiride.

In a further embodiment of the invention, the compound of the formula I is administered in combination with a solid combination of pioglitazone hydrochloride with an angiotensin II agonist, for example TAK-536.

In one embodiment of the invention, the compound of the formula I is administered in combination with a PPAR alpha agonist or mixed PPAR alpha/PPAR delta agonist, for example GW9578, GW-590735, K-111, LY-674, KRP-101, DRF-10945, LY-518674, CP-900691, BMS-687453, BMS-711939, or those as described in WO2001040207, WO2002096894, WO2005097076, WO2007056771, WO2007087448, WO2007089667, WO2007089557, WO2007102515, WO2007103252, JP2007246474, WO2007118963, WO2007118964, WO2007126043, WO2008006043, WO2008006044, WO2008012470, WO2008035359.

In one embodiment of the invention, the compound of the formula I is administered in combination with a mixed PPAR alpha/gamma agonisn, for example naveglitazar, LY-510929, ONO-5129, E-3030, AVE 8042, AVE 8134, AVE 0847, CKD-501 (lobeglitazone sulfate), MBX-213, KY-201 or as described in WO 00/64888, WO 00/64876, WO03/020269,

WO2004024726, WO2007099553, US2007276041, WO2007085135, WO2007085136, WO2007141423, WO2008016175, WO2008053331 or in J. P. Berger et al., TRENDS in Pharmacological Sciences 28(5), 244-251, 2005.

In one embodiment of the invention, the compound of the formula I is administered in combination with a PPAR delta agonist, for example GW-501516, or as described in WO2006059744, WO2006084176, WO2006029699, WO2007039172-WO2007039178, WO2007071766, WO2007101864, US2007244094, WO2007119887, WO2007141423, US2008004281, WO2008016175.

In one embodiment of the invention, the compound of the formula I is administered in combination with a pan-SP-PARM (selective PPAR modulator alpha, gamma, delta), for example GFT-505, or those as described in WO2008035359.

In one embodiment, the compound of the formula I is administered in combination with metaglidasen or with MBX-2044 or other partial PPAR gamma agonists/antagonists.

In one embodiment, the compound of the formula I is administered in combination with an α-glucosidase inhibitor, for example miglitol or acarbose, or those as described, for example, in WO2007114532, WO2007140230, US2007287674, US2008103201.

In one embodiment, the compound of the formula I is administered in combination with an inhibitor of glycogen phosphorylase, for example PSN-357 or FR-258900, or those as described in WO2003084922, WO2004007455, WO2005073229-31, WO2005067932.

In one embodiment, the compound of the formula I is administered in combination with glucagon receptor antagonists, for example A-770077 or NNC-25-2504 or as described in WO2004100875, WO2005065680, WO2006086488, WO2007047177, WO2007106181, WO2007111864, WO2007120270, WO2007120284, WO2007123581, WO2007136577, WO2008042223.

In a further embodiment, the compound of the formula I is administered in combination with an antisense compound, e.g. ISIS-325568, which inhibits the production of the glucagon receptor.

In one embodiment, the compound of the formula I is administered in combination with activators of glucokinase, for example LY-2121260 (WO2004063179), PSN-105, PSN-110, GKA-50, or those as described, for example, in WO2004072031, WO2004072066, WO2005080360, WO2005044801, WO2006016194, WO2006058923, WO2006112549, WO2006125972, WO2007017549, WO2007017649, WO2007007910, WO2007007040-42, WO2007006760-61, WO2007006814, WO2007007886, WO2007028135, WO2007031739, WO2007041365, WO2007041366, WO2007037534, WO2007043638, WO2007053345, WO2007051846, WO2007051845, WO2007053765, WO2007051847, WO2007061923, WO2007075847, WO2007089512, WO2007104034, WO2007117381, WO2007122482, WO2007125103, WO2007125105, US2007281942, WO2008005914, WO2008005964, WO2008043701, WO2008044777, WO2008047821, US2008096877, WO2008050117, WO2008050101, WO2008059625.

In one embodiment, the compound of the formula I is administered in combination with an inhibitor of gluconeogenesis, as described, for example, in FR-225654, WO2008053446.

In one embodiment, the compound of the formula I is administered in combination with inhibitors of fructose 1,6-bisphosphatase (FBPase), for example MB-07729, CS-917 (MB-06322) or MB-07803, or those as described in WO2006023515, WO2006104030, WO2007014619, WO2007137962, WO2008019309, WO2008037628.

In one embodiment, the compound of the formula I is administered in combination with modulators of glucose transporters 4 (GLUT4), for example KST-48 (D.-O. Lee et al.: Arzneim.-Forsch. Drug Res. 54 (12), 835 (2004)).

In one embodiment, the compound of the formula I is administered in combination with inhibitors of glutamine: fructose-6-phosphate amidotransferase (GFAT), as described, for example, in WO2004101528.

In one embodiment, the compound of the formula I is administered in combination with inhibitors of dipeptidyl peptidase IV (DPP-IV), for example vildagliptin (LAF-237), sitagliptin (MK-0431), sitagliptin phosphate, saxagliptin ((BMS-477118), GSK-823093, PSN-9301, SYR-322, SYR-619, TA-6666, TS-021, GRC-8200 (Melogliptin), GW-825964×, KRP-104, DP-893, ABT-341, ABT-279 or another salt thereof, S-40010, S-40755, PF-00734200, BI-1356, PHX-1149, alogliptin, or those compounds as described in WO2003074500, WO2003106456, WO2004037169, WO200450658, WO2005037828, WO2005058901, WO2005012312, WO2005/012308, WO2006039325, WO2006058064, WO2006015691, WO2006015701, WO2006015699, WO2006015700, WO2006018117, WO2006099943, WO2006099941, JP2006160733, WO2006071752, WO2006065826, WO2006078676, WO2006073167, WO2006068163, WO2006085685, WO2006090915, WO2006104356, WO2006127530, WO2006111261, US2006890898, US2006803357, US2006303661, WO2007015767 (LY-2463665), WO2007024993, WO2007029086, WO2007063928, WO2007070434, WO2007071738, WO2007071576, WO2007077508, WO2007087231, WO2007097931, WO2007099385, WO2007100374, WO2007112347, WO2007112669, WO2007113226, WO2007113634, WO2007115821, WO2007116092, US2007259900, EP1852108, US2007270492, WO2007126745, WO2007136603, WO2007142253, WO2007148185, WO2008017670, US2008051452, WO2008027273, WO2008028662, WO2008029217, JP2008031064, JP2008063256, WO2008033851, WO2008040974, WO2008040995, WO2008064107.

In one embodiment, the compound of the formula I is administered in combination with Janumet™, a solid combination of sitagliptin phosphate with metformin hydrochloride.

In one embodiment, the compound of the formula I is administered in combination with Eucreas®, a solid combination of vildagliptin with metformin hydrochloride.

In one embodiment, the compound of the formula I is administered in combination with a solid combination of a salt of sitagliptin with metformin hydrochloride.

In one embodiment, the compound of the formula I is administered in combination with a combination of a DPP-IV inhibitors with omega-3 fatty acids or omega-3 fatty acid esters, as described, for example, in WO2007128801.

In one embodiment, the compound of the formula I is administered in combination with a substance which enhances insulin secretion, for example KCP-265 (WO2003097064), or those as described in WO2007026761, WO2008045484.

In one embodiment, the compound of the formula I is administered in combination with agonists of the glucose-dependent insulinotropic receptor (GDIR), for example APD-668.

In one embodiment of the invention, the compound of the formula I is administered in combination with an ATP citrate lyase inhibitor, for example SB-204990.

In one embodiment, the compound of the formula I is administered in combination with modulators of the sodium-dependent glucose transporter 1 or 2 (SGLT1, SGLT2), for example KGA-2727, T-1095, SGL-0010, AVE 2268, SAR 7226, SGL-5083, SGL-5085, SGL-5094, ISIS-388626, sergliflozin or dapagliflozin, or as described, for example, in WO2004007517, WO200452903, WO200452902, PCT/EP2005/005959, WO2005085237, JP2004359630, WO2005121161, WO2006018150, WO2006035796, WO2006062224, WO2006058597, WO2006073197, WO2006080577, WO2006087997, WO2006108842, WO2007000445, WO2007014895, WO2007080170, WO2007093610, WO2007126117, WO2007128480, WO2007129668, US2007275907, WO2007136116, WO2007143316, WO2007147478, WO2008001864, WO2008002824, WO2008013277, WO2008013280, WO2008013321, WO2008013322, WO2008016132, WO2008020011, JP2008031161, WO2008034859, WO2008042688, WO2008044762, WO2008046497, WO2008049923, WO2008055870, WO2008055940 or by A. L. Handlon in Expert Opin. Ther. Patents (2005) 15(11), 1531-1540.

In one embodiment, the compound of the formula I is administered in combination with inhibitors of 11-beta-hydroxysteroid dehydrogenase 1 (11β-HSD1), for example BVT-2733, JNJ-25918646, INCB-13739, INCB-20817, D10-92 ((−)-ketoconazole) or those as described, for example, in WO200190090-94, WO200343999, WO2004112782, WO200344000, WO200344009, WO2004112779, WO2004113310, WO2004103980, WO2004112784, WO2003065983, WO2003104207, WO2003104208, WO2004106294, WO2004011410, WO2004033427, WO2004041264, WO2004037251, WO2004056744, WO2004058730, WO2004065351, WO2004089367, WO2004089380, WO2004089470-71, WO2004089896, WO2005016877, WO2005063247, WO2005097759, WO2006010546, WO2006012227, WO2006012173, WO2006017542, WO2006034804, WO2006040329, WO2006051662, WO2006048750, WO2006049952, WO2006048331, WO2006050908, WO2006024627, WO2006040329, WO2006066109, WO2006074244, WO2006078006, WO2006106423, WO2006132436, WO2006134481, WO2006134467, WO2006135795, WO2006136502, WO2006138508, WO2006138695, WO2006133926, WO2007003521, WO2007007688, US2007066584, WO2007029021, WO2007047625, WO2007051811, WO2007051810, WO2007057768, WO2007058346, WO2007061661, WO2007068330, WO2007070506, WO2007087150, WO2007092435, WO2007089683, WO2007101270, WO2007105753, WO2007107470, WO2007107550, WO2007111921, US2007207985, US2007208001, WO2007115935, WO2007118185, WO2007122411, WO2007124329, WO2007124337, WO2007124254, WO2007127688, WO2007127693, WO2007127704, WO2007127726, WO2007127763, WO2007127765, WO2007127901, US2007270424, JP2007291075, WO2007130898, WO2007135427, WO2007139992, WO2007144394, WO2007145834, WO2007145835, WO2007146761, WO2008000950, WO2008000951, WO2008003611, WO2008005910, WO2008006702, WO2008006703, WO2008011453, WO2008012532, WO2008024497, WO2008024892, WO2008032164, WO2008034032, WO2008043544, WO2008044656, WO2008046758, WO2008052638, WO2008053194.

In one embodiment, the compound of the formula I is administered in combination with inhibitors of protein tyrosine phosphatase 1B (PTP-1B), as described, for example, in WO200119830-31, WO200117516, WO2004506446, WO2005012295, WO2005116003, WO2005116003, WO2006007959, DE 10 2004 060542.4, WO2007009911, WO2007028145, WO2007067612-615, WO2007081755, WO2007115058, US2008004325, WO2008033455, WO2008033931, WO2008033932, WO2008033934.

In one embodiment of the invention, the compound of the formula I is administered in combination with an agonist of GPR109A (HM74A receptor agonists; NAR agonists (nicotinic acid receptor agonists)), for example nicotinic acid or "extended release niacin" in conjunction with MK-0524A (laropiprant) or MK-0524, or those compounds as described in WO2004041274, WO2006045565, WO2006045564, WO2006069242, WO2006085108, WO2006085112, WO2006085113, WO2006124490, WO2006113150, WO2007017261, WO2007017262, WO2007017265, WO2007015744, WO2007027532, WO2007092364, WO2007120575, WO2007134986, WO2007150025, WO2007150026, WO2008016968, WO2008051403.

In another embodiment of the invention, the compound of the formula I is administered in combination with a solid combination of niacin with simvastatin.

In another embodiment of the invention, the compound of the formula I is administered in combination with nicotinic acid or "extended release niacin" in conjunction with MK-0524A (laropiprant).

In a further embodiment of the invention, the compound of the formula I is administered in combination with nicotinic acid or "extended release niacin" in conjunction with MK-0524A (laropiprant) and with simvastatin.

In one embodiment of the invention, the compound of the formula I is administered in combination with nicotinic acid or another nicotinic acid receptor agonist and a prostaglandin DP receptor antagonist, for example those as described in WO2008039882.

In another embodiment of the invention, the compound of the formula I is administered in combination with an agonist of GPR116, as described, for example, in WO2006067531, WO2006067532.

In one embodiment, the compound of the formula I is administered in combination with modulators of GPR40, as described, for example, in WO2007013689, WO2007033002, WO2007106469, US2007265332, WO2007123225, WO2007131619, WO2007131620, WO2007131621, US2007265332, WO2007131622, WO2007136572, WO2008001931, WO2008030520, WO2008030618, WO2008054674, WO2008054675.

In one embodiment, the compound of the formula I is administered in combination with modulators of GPR119 (G-protein-coupled glucose-dependent insulinotropic receptor), for example PSN-119-1, PSN-821, MBX-2982, or those as described, for example, in WO2005061489 (PSN-632408), WO2004065380, WO2007003960-62 and WO2007003964, WO2007116229, WO2007116230, WO2008005569, WO2008005576, WO2008008887, WO2008008895, WO2008025798, WO2008025799, WO2008025800, WO2007035355, WO2006083491, WO200807692, WO2008076243.

In a further embodiment, the compound of the formula I is administered in combination with modulators of GPR120, as described, for example, in EP1688138.

In one embodiment, the compound of the formula I is administered in combination with inhibitors of hormone-sensitive lipase (HSL) and/or phospholipases, as described, for example, in WO2005073199, WO2006074957, WO2006087309, WO2006111321, WO2007042178, WO2007119837.

In one embodiment, the compound of the formula I is administered in combination with inhibitors of endothelial lipase, as described, for example, in WO2006111321, WO2006131233, WO2006131232, WO2006131231, WO2007042178, WO2007045392, WO2007045393, WO2007110216, WO2007110215.

In one embodiment, the compound of the formula I is administered in combination with a phospholipase A2 inhibitor, for example darapladib or A-002, or those as described in WO2008048866, WO20080488867.

In one embodiment, the compound of the formula I is administered in combination with myricitrin, a lipase inhibitor (WO2007119827).

In one embodiment, the compound of the formula I is administered in combination with an inhibitor of glycogen synthase kinase-3 beta (GSK-3 beta), as described, for example, in US2005222220, WO2005085230, WO2005111018, WO2003078403, WO2004022544, WO2003106410, WO2005058908, US2005038023, WO2005009997, US2005026984, WO2005000836, WO2004106343, EP1460075, WO2004014910, WO2003076442, WO2005087727, WO2004046117, WO2007073117, WO2007083978, WO2007120102, WO2007122634, WO2007125109, WO2007125110, US2007281949, WO2008002244, WO2008002245, WO2008016123, WO2008023239, WO2008044700, WO2008056266, WO2008057940.

In one embodiment, the compound of the formula I is administered in combination with an inhibitor of phosphoenolpyruvate carboxykinase (PEPCK), for example those as described in WO2004074288.

In one embodiment, the compound of the formula I is administered in combination with an inhibitor of phosphoinositide kinase-3 (PI3K), for example those as described in WO2008027584.

In one embodiment, the compound of the formula I is administered in combination with an inhibitor of serum/glucocorticoid-regulated kinase (SGK), as described, for example, in WO2006072354, WO2007093264, WO2008009335.

In one embodiment, the compound of the formula I is administered in combination with a modulator of the glucocorticoid receptor, as described, for example, in WO2008057855, WO2008057856, WO2008057857, WO2008057859, WO2008057862.

In one embodiment, the compound of the formula I is administered in combination with an inhibitor of protein kinase C beta (PKC beta), for example ruboxistaurin.

In a further embodiment, the compound of the formula I is administered in combination with an activator of the AMP-activated protein kinase (AMPK), as described, for example, in WO2007062568, WO2008006432, WO2008016278, WO2008016730.

In one embodiment, the compound of the formula I is administered in combination with an inhibitor of ceramide kinase, as described, for example, in WO2007112914, WO2007149865.

In a further embodiment, the compound of the formula I is administered in combination with an inhibitor of MAPK-interacting kinase 1 or 2 (MNK1 or 2), as described, for example, in WO2007104053, WO2007115822, WO2008008547.

In one embodiment, the compound of the formula I is administered in combination with inhibitors of "I-kappaB kinase" (IKK inhibitors), as described, for example, in WO2001000610, WO2001030774, WO2004022057, WO2004022553, WO2005097129, WO2005113544, US2007244140.

In another embodiment, the compound of the formula I is administered in combination with inhibitors of NF-kappaB (NFKB) activation, for example salsalate.

In a further embodiment, the compound of the formula I is administered in combination with inhibitors of ASK-1 (apoptosis signal-regulating kinase 1), as described, for example, in WO2008016131.

In one embodiment of the invention, the compound of the formula I is administered in combination with an HMG-CoA reductase inhibitor such as simvastatin, fluvastatin, pravastatin, lovastatin, atorvastatin, cerivastatin, rosuvastatin, L-659699, BMS-644950, or those as described in US2007249583.

In a further embodiment of the invention, the compound of the formula I is administered in combination with a farnesoid X receptor (FXR) modulator, for example WAY-362450 or those as described in WO2003099821, WO2005056554, WO2007052843, WO2007070796, WO2007092751, JP2007230909, WO2007095174, WO2007140174, WO2007140183, WO2008000643, WO2008002573, WO2008025539, WO2008025540.

In another embodiment of the invention, the compound of the formula I is administered in combination with a ligand of the liver X receptor (LXR), as described, for example, in WO2007092965, WO2008041003, WO2008049047.

In one embodiment of the invention, the compound of the formula I is administered in combination with a fibrate, for example fenofibrate, clofibrate, bezafibrate.

In one embodiment of the invention, the compound of the formula I is administered in combination with fibrates, for example the choline salt of fenofibrate (SLV-348).

In one embodiment of the invention, the compound of the formula I is administered in combination with fibrates, for example the choline salt of fenofibrate and an HMG-CoA reductase inhibitor, for example rosuvastatin.

In a further embodiment of the invention, the compound of the formula I is administered in combination with bezafibrate and diflunisal.

In a further embodiment of the invention, the compound of the formula I is administered in combination with a solid combination of fenofibrate or a salt thereof with simvastatin, rosuvastatin, fluvastatin, lovastatin, cerivastatin, pravastatin or atorvastatin.

In a further embodiment of the invention, the compound of the formula I is administered in combination with Synordia®, a solid combination of fenofibrate with metformin.

In one embodiment of the invention, the compound of the formula I is administered in combination with a cholesterol reabsorption inhibitor, for example ezetimibe, tiqueside, pamaqueside, FM-VP4 (sitostanol/campesterol ascorbyl phosphate; Forbes Medi-Tech, WO2005042692, WO2005005453), MD-0727 (Microbia Inc., WO2005021497, WO2005021495) or with compounds as described in WO2002066464, WO2005000353 (Kotobuki Pharmaceutical Co. Ltd.) or WO2005044256 or WO2005062824 (Merck & Co.) or WO2005061451 and WO2005061452 (AstraZeneca AB) and WO2006017257 (Phenomix) or WO2005033100 (Lipideon Biotechnology

AG), or as described in WO2002050060, WO2002050068, WO2004000803, WO2004000804, WO2004000805, WO2004087655, WO2004097655, WO2005047248, WO2006086562, WO2006102674, WO2006116499, WO2006121861, WO2006122186, WO2006122216, WO2006127893, WO2006137794, WO2006137796, WO2006137782, WO2006137793, WO2006137797, WO2006137795, WO2006137792, WO2006138163, WO2007059871, US2007232688, WO2007126358, WO2008033431, WO2008033465, WO2008052658, WO2008057336.

In one embodiment of the invention, the compound of the formula I is administered in combination with an NPC1L1 antagonist, for example those as described in WO2008033464, WO2008033465.

In one embodiment of the invention, the compound of the formula I is administered in combination with Vytorin™, a solid combination of ezetimibe with simvastatin.

In one embodiment of the invention, the compound of the formula I is administered in combination with a solid combination of ezetimibe with atorvastatin.

In one embodiment of the invention, the compound of the formula I is administered in combination with a solid combination of ezetimibe with fenofibrate.

In one embodiment of the invention, the further active ingredient is a diphenylazetidinone derivative, as described, for example, in U.S. Pat. Nos. 6,992,067 or 7,205,290.

In a further embodiment of the invention, the further active ingredient is a diphenylazetidinone derivative, as described, for example, in U.S. Pat. Nos. 6,992,067 or 7,205,290, combined with a statin, for example simvastatin, fluvastatin, pravastatin, lovastatin, cerivastatin, atorvastatin or rosuvastatin.

In one embodiment of the invention, the compound of the formula I is administered in combination with a solid combination of lapaquistat, a squalene synthase inhibitor, with atorvastatin.

In one embodiment of the invention, the compound of the formula I is administered in combination with a CETP inhibitor, for example torcetrapib, anacetrapib or JTT-705 (dalcetrapib), or those as described in WO2006002342, WO2006010422, WO2006012093, WO2006073973, WO2006072362, WO2007088996, WO2007088999, US2007185058, US2007185113, US2007185154, US2007185182, WO2006097169, WO2007041494, WO2007090752, WO2007107243, WO2007120621, US2007265252, US2007265304, WO2007128568, WO2007132906, WO2008006257, WO2008009435, WO2008018529, WO2008058961, WO2008058967.

In one embodiment of the invention, the compound of the formula I is administered in combination with bile acid reabsorption inhibitor (see, for example, U.S. Pat. Nos. 6,245,744, 6,221,897 or WO00/61568), for example HMR 1741, or those as described in DE 10 2005 033099.1 and DE 10 2005 033100.9, DE 10 2006 053635, DE 10 2006 053637, WO2007009655-56, WO2008058628, WO2008058629, WO2008058630, WO2008058631.

In one embodiment, the compound of the formula I is administered in combination with agonists of GPBAR1 (G-protein-coupled bile acid receptor-1; TGR5), as described, for example, in WO2007110237, WO2007127505, WO2008009407.

In one embodiment of the invention, the compound of the formula I is administered in combination with a polymeric bile acid adsorber, for example cholestyramine, colesevelam hydrochloride.

In one embodiment of the invention, the compound of the formula I is administered in combination with colesevelam hydrochloride and metformin or a sulfonylurea or insulin.

In one embodiment of the invention, the compound of the formula I is administered in combination with a chewing gum comprising phytosterols (Reductol™)

In one embodiment of the invention, the compound of the formula I is administered in combination with an inhibitor of the microsomal triglyceride transfer proteins (MTP inhibitor), for example implitapide, BMS-201038, R-103757, AS-1552133, SLx-4090, AEGR-733, or those as described in WO2005085226, WO2005121091, WO2006010423, WO2006113910, WO2007143164, WO2008049806, WO2008049808.

In a further embodiment of the invention, the compound of the formula I is administered in combination with a combination of a cholesterol absorption inhibitor, for example ezetimibe, and an inhibitor of the triglyceride transfer proteins (MTP inhibitor), for example implitapide, as described in WO2008030382.

In one embodiment of the invention, the compound of the formula I is administered in combination with an active antihypertriglyceridemic ingredient, for example those as described in WO2008032980.

In another embodiment of the invention, the compound of the formula I is administered in combination with an antagonist of the somatostatin 5 receptor (SST5 receptor), for example those as described in WO2006094682.

In one embodiment of the invention, the compound of the formula I is administered in combination with an ACAT inhibitor, for example avasimibe, SMP-797 or KY-382.

In a further embodiment of the invention, the compound of the formula I is administered in combination with an inhibitor of liver carnitine palmitoyltransferase 1 (L-CPT1), as described, for example, in WO2007063012, WO2007096251 (ST-3473), WO2008015081, US2008103182.

In a further embodiment of the invention, the compound of the formula I is administered in combination with a modulator of serine palmitoyltransferase (SPT), as described, for example, in WO2008031032, WO2008046071.

In one embodiment of the invention, the compound of the formula I is administered in combination with a squalene synthetase inhibitor, for example BMS-188494, TAK-475 (lapaquistat acetate), or as described in WO2005077907, JP2007022943, WO2008003424.

In one embodiment of the invention, the compound of the formula I is administered in combination with ISIS-301012 (mipomersen), an antisense oligonucleotide which is capable of regulating the apolipoprotein B gene.

In one embodiment of the invention, the compound of the formula I is administered in combination with an LDL receptor inducer (see U.S. Pat. No. 6,342,512), for example HMR1171, HMR1586, or those as described in WO2005097738, WO2008020607.

In another embodiment of the invention, the compound of the formula I is administered in combination with an HDL cholesterol-elevating agent, for example those as described in WO2008040651.

In one embodiment of the invention, the compound of the formula I is administered in combination with an ABCA1 expression enhancer, as described, for example, in WO2006072393.

In one embodiment of the invention, the compound of the formula I is administered in combination with a lipoprotein-lipase modulator, for example ibrolipim (NO-1886).

In one embodiment of the invention, the compound of the formula I is administered in combination with a lipoprotein (a) antagonist, for example gemcabene (CI-1027).

In one embodiment of the invention, the compound of the formula I is administered in combination with a lipase inhibitor, for example orlistat or cetilistat (ATL-962).

In one embodiment of the invention, the compound of the formula I is administered in combination with an adenosine A1 receptor agonist (adenosine A1 R), as described, for example, in EP1258247, EP1375508, WO2008028590.

In one embodiment of the invention, the compound of the formula I is administered in combination with an adenosine A2B receptor agonist (adenosine A2B R), for example ATL-801.

In another embodiment of the invention, the compound of the formula I is administered in combination with a modulator of adenosine A2A and/or adenosine A3 receptors, as described, for example, in WO2007111954, WO2007121918, WO2007121921, WO2007121923.

In one embodiment of the invention, the compound of the formula I is administered in combination with an adenosine A2B receptor antagonist (adenosine A2B R), as described in US2007270433, WO2008027585.

In one embodiment, the compound of the formula I is administered in combination with inhibitors of acetyl-CoA carboxylase (ACC1 and/or ACC2), for example those as described in WO199946262, WO200372197, WO2003072197, WO2005044814, WO2005108370, JP2006131559, WO2007011809, WO2007011811, WO2007013691, WO2007095601-603, WO2007119833.

In another embodiment, the compound of the formula I is administered in combination with modulators of microsomal acyl-CoA:glycerol-3-phosphate acyltransferase 3 (GPAT3, described in WO2007100789) or with modulators of microsomal acyl-CoA:glycerol-3-phosphate acyltransferase 4 (GPAT4, described in WO2007100833).

In a further embodiment, the compound of the formula I is administered in combination with modulators of xanthine oxidoreductase (XOR).

In another embodiment, the compound of the formula I is administered in combination with inhibitors of soluble epoxide hydrolase (sEH), as described, for example, in WO2008051873, WO2008051875.

In a further embodiment, the compound of the formula I is administered in combination with CART modulators (see "Cocaine-amphetamine-regulated transcript influences energy metabolism, anxiety and gastric emptying in mice" Asakawa, A. et al.: Hormone and Metabolic Research (2001), 33(9), 554-558);

NPY antagonists, for example N-{4-[(4-aminoquinazolin-2-ylamino)methyl]-cyclohexylmethyl}naphthalene-1-sulfonamide hydrochloride (CGP 71683A);

NPY-5 receptor antagonists, such as L-152804 or the compound "NPY-5-BY" from Banyu, or as described, for example, in WO2006001318, WO2007103295, WO2007125952, WO2008026563, WO2008026564, WO2008052769;

NPY-4 receptor antagonists, as described, for example, in WO2007038942;

NPY-2 receptor antagonists, as described, for example, in WO2007038943;

peptide YY 3-36 (PYY3-36) or analogous compounds, for example CJC-1682 (PYY3-36 conjugated with human serum albumin via Cys34) or CJC-1643 (derivative of PYY3-36, which is conjugated in vivo to serum albumin), or those as described in WO2005080424, WO2006095166, WO2008003947;

derivatives of the peptide obestatin, as described by WO2006096847;

CB1R (cannabinoid receptor 1) antagonists, for example rimonabant, surinabant (SR147778), SLV-319 (ibipinabant), AVE-1625, taranabant (MK-0364) or salts thereof, otenabant (CP-945,598), V-24343 or those compounds as described in, for example, EP 0656354, WO 00/15609, WO2001/64632-64634, WO 02/076949, WO2005080345, WO2005080328, WO2005080343, WO2005075450, WO2005080357, WO200170700, WO2003026647-48, WO200302776, WO2003040107, WO2003007887, WO2003027069, U.S. Pat. No. 6,509,367, WO200132663, WO2003086288, WO2003087037, WO2004048317, WO2004058145, WO2003084930, WO2003084943, WO2004058744, WO2004013120, WO2004029204, WO2004035566, WO2004058249, WO2004058255, WO2004058727, WO2004069838, US20040214837, US20040214855, US20040214856, WO2004096209, WO2004096763, WO2004096794, WO2005000809, WO2004099157, US20040266845, WO2004110453, WO2004108728, WO2004000817, WO2005000820, US20050009870, WO200500974, WO2004111033-34, WO200411038-39, WO2005016286, WO2005007111, WO2005007628, US20050054679, WO2005027837, WO2005028456, WO2005063761-62, WO2005061509, WO2005077897, WO2006018662, WO2006047516, WO2006060461, WO2006067428, WO2006067443, WO2006087480, WO2006087476, WO2006100208, WO2006106054, WO2006111849, WO2006113704, WO2007009705, WO2007017124, WO2007017126, WO2007018459, WO2007018460, WO2007016460, WO2007020502, WO2007026215, WO2007028849, WO2007031720, WO2007031721, WO2007036945, WO2007038045, WO2007039740, US20070015810, WO2007046548, WO2007047737, WO2007057687, WO2007062193, WO2007064272, WO2007079681, WO2007084319, WO2007084450, WO2007086080, EP1816125, US2007213302, WO2007095513, WO2007096764, US2007254863, WO2007119001, WO2007120454, WO2007121687, WO2007123949, US2007259934, WO2007131219, WO2007133820, WO2007136571, WO2007136607, WO2007136571, U.S. Pat. No. 7,297,710, WO2007138050, WO2007139464, WO2007140385, WO2007140439, WO2007146761, WO2007148061, WO2007148062, US2007293509, WO2008004698, WO2008017381, US2008021031, WO2008024284, WO2008031734, WO2008032164, WO2008034032, WO2008035356, WO2008036021, WO2008036022, WO2008039023, WO2998043544, WO2008044111, WO2008048648, EP 1921072-A1, WO2008053341, WO2008056377, WO2008059207, WO2008059335;

cannabinoid receptor 1/cannabinoid receptor 2 (CB1/CB2) modulating compounds, for example delta-9-tetrahydrocannabivarin, or those as described, for example, in WO2007001939, WO2007044215, WO2007047737, WO2007095513, WO2007096764, WO2007112399, WO2007112402;

modulators of FAAH (fatty acid amide hydrolase), as described, for example, in WO2007140005, WO2008019357, WO2008021625, WO2008023720, WO2008030532;

vanilloid-1 receptor modulators (modulators of TRPV1), as described, for example, in WO2007091948, WO2007129188, WO2007133637, WO2008007780, WO2008010061, WO2008007211, WO2008010061,

WO2008015335, WO2008018827, WO2008024433, WO2008024438, WO2008032204, WO2008050199, WO2008059370;

antagonists or inverse agonists of the opioid receptors, as described, for example, in WO2008021849, WO2008021851, WO2008032156;

agonists of the prostaglandin receptor, for example bimatoprost or those compounds as described in WO2007111806;

MC4 receptor agonists (melanocortin-4 receptor agonists, MC4R agonists, for example N-[2-(3a-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydropyrazolo[4,3-c]-pyridin-5-yl)-1-(4-chlorophenyl)-2-oxoethyl]-1-amino-1,2,3,4-tetrahydronaphthalene-2-carboxamide; (WO 01/91752)) or LB53280, LB53279, LB53278 or THIQ, MB243, RY764, CHIR-785, PT-141, MK-0493, or those as described in WO2005060985, WO2005009950, WO2004087159, WO2004078717, WO2004078716, WO2004024720, US20050124652, WO2005051391, WO2004112793, WOUS20050222014, US20050176728, US20050164914, US20050124636, US20050130988, US20040167201, WO2004005324, WO2004037797, WO2005042516, WO2005040109, WO2005030797, US20040224901, WO200501921, WO200509184, WO2005000339, EP1460069, WO2005047253, WO2005047251, WO2005118573, EP1538159, WO2004072076, WO2004072077, WO2006021655-57, WO2007009894, WO2007015162, WO2007041061, WO2007041052, JP2007131570, EP-1842846, WO2007096186, WO2007096763, WO2007141343, WO2008007930, WO2008017852, WO2008039418;

orexin receptor 1 antagonists (OX1R antagonists), orexin receptor 2 antagonists (OX2R antagonists) or mixed OX1R/OX2R antagonists (e.g. 1-(2-methyl-benzoxazol-6-yl)-3-[1,5]naphthyridin-4-ylurea hydrochloride (SB-334867-A), or those as described, for example, in WO200196302, WO200185693, WO2004085403, WO2005075458, WO2006067224, WO2007085718, WO2007088276, WO2007116374; WO2007122591, WO2007126934, WO2007126935, WO2008008517, WO2008008518, WO2008008551, WO2008020405, WO2008026149, WO2008038251);

histamine H3 receptor antagonists/inverse agonists (e.g. 3-cyclohexyl-1-(4,4-dimethyl-1,4,6,7-tetrahydroimidazo[4,5-c]pyridin-5-yl)propan-1-one oxalic acid salt (WO 00/63208), or those as described in WO200064884, WO2005082893, US2005171181 (e.g. PF-00389027), WO2006107661, WO2007003804, WO2007016496, WO2007020213, WO2007049798, WO2007055418, WO2007057329, WO2007065820, WO2007068620, WO2007068641, WO2007075629, WO2007080140, WO2007082840, WO2007088450, WO2007088462, WO2007094962, WO2007099423, WO2007100990, WO2007105053, WO2007106349, WO2007110364, WO2007115938, WO2007131907, WO2007133561, US2007270440, WO2007135111, WO2007137955, US2007281923, WO2007137968, WO2007138431, WO2007146122, WO2008005338, WO2008012010, WO2008015125, WO2008045371);

histamine H1/histamine H3 modulators, for example betahistine or its dihydrochloride;

modulators of the histamine H3 transporter or of the histamine H3/serotonin transporter, as described, for example, in WO2008002816, WO2008002817, WO2008002818, WO2008002820;

histamine H4 modulators, as described, for example, in WO2007117399;

CRF antagonists (e.g. [2-methyl-9-(2,4,6-trimethylphenyl)-9H-1,3,9-triazafluoren-4-yl]dipropylamine (WO 00/66585) or those CRF1 antagonists as described in WO2007105113, WO2007133756, WO2008036541, WO2008036579);

CRF BP antagonists (e.g. urocortin);

urocortin agonists;

agonists of the beta-3 adrenoceptor, for example 1-(4-chloro-3-methanesulfonylmethylphenyl)-2-[2-(2,3-dimethyl-1H-indol-6-yloxy)ethylamino]-ethanol hydrochloride (WO 01/83451) or solabegron (GW-427353) or N-5984 (KRP-204), or those as described in JP2006111553, WO2002038543, WO2002038544, WO2007048840-843, WO2008015558;

MSH (melanocyte-stimulating hormone) agonists;

MCH (melanine-concentrating hormone) receptor antagonists (for example NBI-845, A-761, A-665798, A-798, ATC-0175, T-226296, T-71 (AMG-071, AMG-076), GW-803430, GW-856464, NGD-4715, ATC-0453, ATC-0759 or those compounds as described in WO2005085200, WO2005019240, WO2004011438, WO2004012648, WO2003015769, WO2004072025, WO2005070898, WO2005070925, WO2004039780, WO2004092181, WO2003033476, WO2002006245, WO2002089729, WO2002002744, WO2003004027, FR2868780, WO2006010446, WO2006038680, WO2006044293, WO2006044174, JP2006176443, WO2006018280, WO2006018279, WO2006118320, WO2006130075, WO2007018248, WO2007012661, WO2007029847, WO2007024004, WO2007039462, WO2007042660, WO2007042668, WO2007042669, US2007093508, US2007093509, WO2007048802, JP2007091649, WO2007092416; WO2007093363-366, WO2007114902, WO2007114916, WO2007141200, WO2007142217, US2007299062, WO2007146758, WO2007146759, WO200800116, WO2008016811, WO2008020799, WO2008022979, WO2008038692, WO2008041090, WO2008044632, WO2008047544, JP2008088120, WO2008065021, WO2008068265, WO2008061109, WO2008076562, WO2008071646);

CCK-A (CCK-1) agonists (for example {2-[4-(4-chloro-2,5-dimethoxyphenyl)-5-(2-cyclohexylethyl)thiazol-2-ylcarbamoyl]-5,7-dimethylindol-1-yl}acetic acid trifluoro-acetic acid salt (WO 99/15525) or SR-146131 (WO 0244150) or SSR-125180), or those as described in WO2005116034, WO2007120655, WO2007120688, WO2007120718;

serotonin reuptake inhibitors (e.g. dexfenfluramine), or those as described in WO2007148341, WO2008034142;

mixed serotonin/dopamine reuptake inhibitors (e.g. bupropion), or those as described in WO2008063673, or solid combinations of bupropion with naltrexone or bupropion with zonisamide;

mixed reuptake inhibitors, for example DOV-21947;

mixed serotoninergic and noradrenergic compounds (e.g. WO 00/71549);

5-HT receptor agonists, for example 1-(3-ethylbenzofuran-7-yl)piperazine oxalic acid salt (WO 01/09111);

mixed dopamine/norepinephrine/acetylcholine reuptake inhibitors (e.g. tesofensine), or those as described, for example, in WO2006085118;

norepinephrine reuptake inhibitors, as described, for example, in US2008076724;

5-HT2A receptor antagonists, as described, for example, in WO2007138343;

5-HT2C receptor agonists (for example lorcaserine hydrochloride (APD-356) or BVT-933, or those as described in WO200077010, WO200077001-02, WO2005019180,

WO2003064423, WO200242304, WO2005035533, WO2005082859, WO2006004937, US2006025601, WO2006028961, WO2006077025, WO2006103511, WO2007028132, WO2007084622, US2007249709; WO2007132841, WO2007140213, WO2008007661, WO2008007664, WO2008009125, WO2008010073);

5-HT6 receptor modulators, for example E-6837, BVT-74316 or PRX-07034, or those as described, for example, in WO2005058858, WO2007054257, WO2007107373, WO2007108569, WO2007108742-744, WO2008003703, WO2008027073, WO2008034815, WO2008054288;

agonists of estrogen receptor gamma (ERRγ agonists), as described, for example, in WO2007131005, WO2008052709;

sigma-1 receptor antagonists, as described, for example, in WO2007098953, WO2007098961, WO2008015266, WO2008055932, WO2008055933;

muscarin 3 receptor (M3R) antagonists, as described, for example, in WO2007110782, WO2008041184;

bombesin receptor agonists (BRS-3 agonists), as described, for example, in WO2008051404, WO2008051405, WO2008051406;

galanin receptor antagonists;

growth hormone (e.g. human growth hormone or AOD-9604);

growth hormone releasing compounds (tert-butyl 6-benzyloxy-1-(2-diisopropylaminoethylcarbamoyl)-3,4-dihydro-1H-isoquinoline-2-carboxylate (WO 01/85695));

growth hormone secretagogue receptor antagonists (ghrelin antagonists), for example A-778193, or those as described in WO2005030734, WO2007127457, WO2008008286;

growth hormone secretagogue receptor modulators, for example JMV-2959, JMV-3002, JMV-2810, JMV-2951, or those as described in WO2006012577 (e.g. YIL-781 or YIL-870), WO2007079239;

TRH agonists (see, for example, EP 0 462 884);

decoupling protein 2 or 3 modulators;

leptin agonists (see, for example, Lee, Daniel W.; Leinung, Matthew C.; Rozhayskaya-Arena, Marina; Grasso, Patricia. Leptin agonists as a potential approach to the treatment of obesity. Drugs of the Future (2001), 26(9), 873-881);

DA agonists (bromocriptin, doprexin);

lipase/amylase inhibitors (e.g. WO 00/40569);

inhibitors of diacylglycerol O-acyltransferases (DGATs), for example BAY-74-4113, or as described, for example, in US2004/0224997, WO2004094618, WO200058491, WO2005044250, WO2005072740, JP2005206492, WO2005013907, WO2006004200, WO2006019020, WO2006064189, WO2006082952, WO2006120125, WO2006113919, WO2006134317, WO2007016538, WO2007060140, JP2007131584, WO2007071966, WO2007126957, WO2007137103, WO2007137107, WO2007138304, WO2007138311, WO2007141502, WO2007141517, WO2007141538, WO2007141545, WO2007144571, WO2008011130, WO2008011131, WO2008039007, WO2008048991;

inhibitors of monoacylglycerol acyltransferase (2-acylglycerol O-acyltransferase; MGAT), as described, for example, in WO2008038768;

inhibitors of fatty acid synthase (FAS), for example C75, or those as described in WO2004005277, WO2008006113;

inhibitors of stearoyl-CoA delta9 desaturase (SCD1), as described, for example, in WO2007009236, WO2007044085, WO2007046867, WO2007046868, WO20070501124, WO2007056846, WO2007071023, WO2007130075, WO2007134457, WO2007136746, WO2007143597, WO2007143823, WO2007143824, WO2008003753, WO2008017161, WO2008024390, WO2008029266, WO2008036715, WO2008043087, WO2008044767, WO2008046226, WO2008056687;

hypoglycemic/hypertriglyceridemic indoline compounds, as described in WO2008039087;

inhibitors of "adipocyte fatty acid-binding protein aP2", for example BMS-309403; activators of adiponectin secretion, as described, for example, in WO2006082978; promoters of adiponectin secretion, as described, for example, in WO2007125946, WO2008038712;

oxyntomodulin or analogs thereof;

oleoyl-estrone

or agonists or partial agonists of the thyroid hormone receptor (thyroid hormone receptor agonists), for example: KB-2115 (eprotirome), QRX-431 (sobetirome) or DITPA, or those as described in WO20058279, WO200172692, WO200194293, WO2003084915, WO2004018421, WO2005092316, WO2007003419, WO2007009913, WO2007039125, WO2007110225, WO2007110226, WO2007128492, WO2007132475, WO2007134864, WO2008001959

or agonists of the thyroid hormone receptor beta (TR-beta), for example MB-07811 or MB-07344.

In one embodiment of the invention, the compound of the formula I is administered in combination with a combination of epotirome with ezetimibe.

In one embodiment of the invention, the compound of the formula I is administered in combination with an inhibitor of site-1 protease (S1P), for example PF-429242.

In a further embodiment of the invention, the compound of the formula I is administered in combination with an RNAi therapeutic agent directed against PCSK9 (proprotein convertase subtilisin/kexin type 9).

In one embodiment, the compound of the formula I is administered in combination with Omacor® or Lovaza™ (omega-3 fatty acid ester; highly concentrated ethyl ester of eicosapentaenoic acid and of docosahexaenoic acid).

In one embodiment, the compound of the formula I is administered in combination with lycopene.

In one embodiment of the invention, the compound of the formula I is administered in combination with an antioxidant, for example OPC-14117, AGI-1067 (succinobucol), probucol, tocopherol, ascorbic acid, β-carotene or selenium.

In one embodiment of the invention, the compound of the formula I is administered in combination with a vitamin, for example Vitamin B6 or Vitamin B12.

In one embodiment, the compound of the formula I is administered in combination with more than one of the aforementioned compounds, for example in combination with a sulfonylurea and metformin, a sulfonylurea and acarbose, repaglinide and metformin, insulin and a sulfonylurea, insulin and metformin, insulin and troglitazone, insulin and lovastatin, etc.

In another embodiment, the compound of the formula I is administered in combination with an inhibitor of carboanhydrase type 2 (carbonic anhydrase type 2), for example those as described in WO2007065948.

In another embodiment, the compound of the formula I is administered in combination with topiramat or a derivative thereof, as described in WO2008027557.

In a further embodiment, the compound of the formula I is administered in combination with a solid combination of topiramat with phentermin (Qnexa™)

In a further embodiment, the compound of the formula I is administered in combination with an antisense compound, e.g. ISIS-377131, which inhibits the production of the glucocorticoid receptor.

In another embodiment, the compound of the formula I is administered in combination with an aldosterone synthase inhibitor and an antagonist of the glucocorticoid receptor, a cortisol synthesis inhibitor and/or an antagonist of the corticotropin releasing factor, as described, for example, in EP1886695.

In one embodiment, the compound of the formula I is administered in combination with an agonist of the RUP3 receptor, as described, for example, in WO2007035355, WO2008005576.

In another embodiment, the compound of the formula I is administered in combination with an activator of the gene which codes for ataxia telangiectasia mutated (ATM) protein kinase, for example chloroquine.

In one embodiment, the compound of the formula I is administered in combination with a tau protein kinase 1 inhibitor (TPK1 inhibitor), as described, for example, in WO2007119463.

In one embodiment, the compound of the formula I is administered in combination with a "c-Jun N-terminal kinase" inhibitor (JNK inhibitor), as described, for example, in WO2007125405, WO2008028860.

In one embodiment, the compound of the formula I is administered in combination with an endothelin A receptor antagonist, for example avosentan (SPP-301).

In one embodiment, the compound of the formula I is administered in combination with modulators of the glucocorticoid receptor (GR), for example KB-3305 or those compounds as described, for example, in WO2005090336, WO2006071609, WO2006135826, WO2007105766.

In one embodiment, the further active ingredient is varenicline tartrate, a partial agonist of the alpha 4-beta 2 nicotinic acetylcholine receptor.

In one embodiment, the further active ingredient is trodusquemine.

In one embodiment, the further active ingredient is a modulator of the enzyme SIRT1 (an NAD^+-dependent protein deacetylase); this active ingredient may, for example, be resveratrol in suitable formulations, or those compounds as specified in WO2007019416 (e.g. SRT-1720).

In one embodiment of the invention, the further active ingredient is DM-71 (N-acetyl-L-cysteine with bethanechol).

In one embodiment, the compound of the formula I is administered in combination with antihypercholesterolemic compounds, as described, for example, in WO2007107587, WO2007111994.

In another embodiment, the compound of the formula I is administered in combination with a cyclic peptide agonist of the VPAC2 receptor, as described, for example, in WO2007101146, WO2007133828.

In a further embodiment, the compound of the formula I is administered in combination with an agonist of the endothelin receptor, as described, for example, in WO2007112069.

In a further embodiment, the compound of the formula I is administered in combination with AKP-020 (bis(ethylmaltolato)oxovanadium (IV)).

In another embodiment, the compound of the formula I is administered in combination with tissue-selective androgen receptor modulators (SARM), as described, for example, in WO2007099200, WO2007137874.

In a further embodiment, the compound of the formula I is administered in combination with an AGE (advanced glycation end product) inhibitor, as described, for example, in JP2008024673.

In one embodiment of the invention, the further active ingredient is leptin; see, for example, "Perspectives in the therapeutic use of leptin", Salvador, Javier; Gomez-Ambrosi, Javier; Fruhbeck, Gema, Expert Opinion on Pharmacotherapy (2001), 2(10), 1615-1622.

In another embodiment of the invention, the further active ingredient is metreleptin (recombinant methionyl-leptin) combined with pramlintide.

In a further embodiment of the invention, the further active ingredient is the tetrapeptide ISF-402.

In one embodiment, the further active ingredient is dexamphetamine or amphetamine.

In one embodiment, the further active ingredient is fenfluramin or dexfenfluramin.

In another embodiment, the further active ingredient is sibutramine or those derivatives as described in WO2008034142.

In one embodiment, the further active ingredient is mazindol or phentermin.

In a further embodiment, the further active ingredient is geniposidic acid (WO2007100104) or derivatives thereof (JP2008106008).

In one embodiment, the further active ingredient is a nasal calcium channel blocker, for example diltiazem, or those as described in U.S. Pat. No. 7,138,107.

In one embodiment, the further active ingredient is an inhibitor of sodium-calcium ion exchange, for example those as described in WO2008028958.

In a further embodiment, the further active ingredient is a blocker of calcium channels, for example of CaV3.2, as described in WO2008033431, WO2008033447, WO2008033356, WO2008033460, WO2008033464, WO2008033465, WO2008033468.

In one embodiment, the further active ingredient is a blocker of the "T-type calcium channel", as described, for example, in WO2008033431.

In one embodiment, the further active ingredient is an inhibitor of KCNQ potassium channel 2 or 3, for example those as described in US2008027049, US2008027090.

In one embodiment, the further active ingredient is an inhibitor of the potassium Kv1.3 ion channel, for example those as described in WO2008040057, WO2008040058, WO2008046065.

In another embodiment, the further active ingredient is a modulator of the MCP-1 receptor (monocyte chemoattractant protein-1 (MCP-1)), for example those as described in WO2008014360, WO2008014381.

In one embodiment, the further active ingredient is a modulator of somatostatin receptor 5 (SSTR5), for example those as described in WO2008019967, US2008064697.

In one embodiment, the further active ingredient is a modulator of somatostatin receptor 2 (SSTR2), for example those as described in WO2008051272.

In one embodiment, the further active ingredient is an erythropoietin-mimetic peptide which acts as an erythropoietin (EPO) receptor agonist. Such molecules are described, for example, in WO2008042800.

In a further embodiment, the further active ingredient is an anorectic/a hypoglycemic compound, for example those as described in WO2008035305, WO2008035306, WO2008035686.

In one embodiment, the further active ingredient is an inductor of lipoic acid synthetase, for example those as described in WO2008036966, WO2008036967.

In one embodiment, the further active ingredient is a stimulator of endothelial nitric oxide synthase (eNOS), for example those as described in WO2008058641.

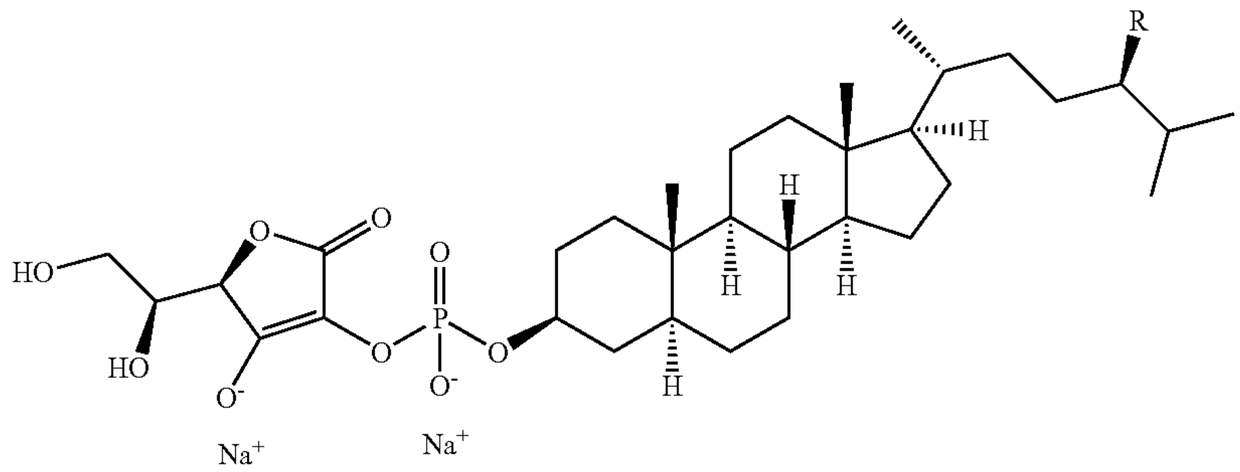
In one embodiment, the further active ingredient is a modulator of carbohydrate and/or lipid metabolism, for example those as described in WO2008059023, WO2008059024, WO2008059025, WO2008059026.

In a further embodiment, the further active ingredient is an angiotensin II receptor antagonist, for example those as described in WO2008062905.

In one embodiment, the further active ingredient is an agonist of the sphingosine-1-phosphate receptor (S1P), for example those as described in WO2008064315.

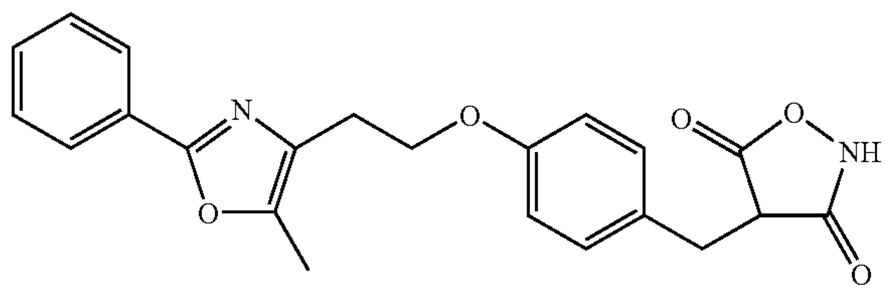
In one embodiment, the compound of the formula I is administered in combination with bulking agents, preferably insoluble bulking agents (see, for example, Carob/Caromax® (Zunft H J; et al., Carob pulp preparation for treatment of hypercholesterolemia, ADVANCES IN THERAPY (2001 September-October), 18(5), 230-6). Caromax is a carob-containing product from Nutrinova, Nutrition Specialties & Food Ingredients GmbH, Industriepark Höchst, 65926 Frankfurt/Main). Combination with Caromax® is possible in one preparation or by separate administration of compounds of the formula I and Caromax®. Caromax® can in this connection also be administered in the form of food products such as, for example, in bakery products or muesli bars.

It will be appreciated that every suitable combination of the compounds of the invention with one or more of the aforementioned compounds and optionally one or more other pharmacologically active substances is regarded as falling within the protection conferred by the present invention.



FM-VP4

R = CH_3; CH_2—CH_3



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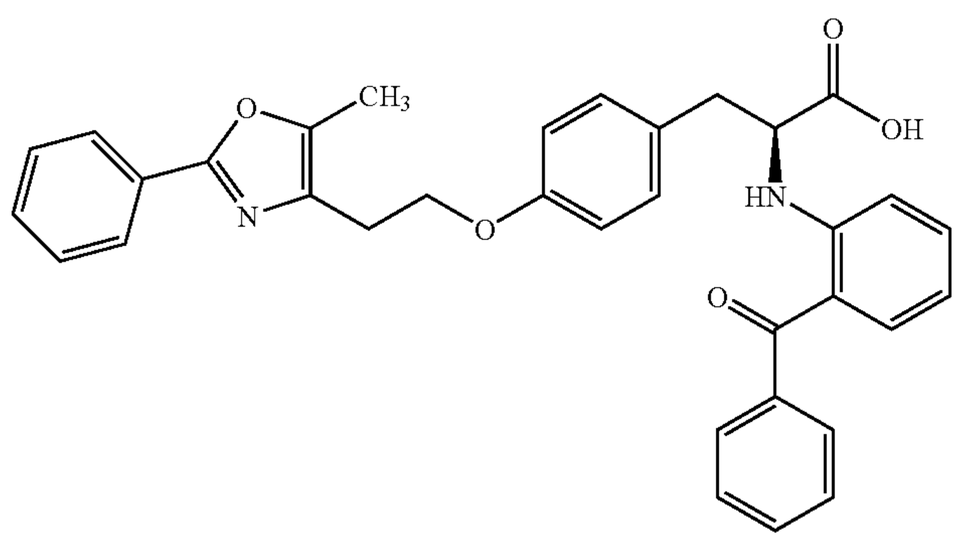

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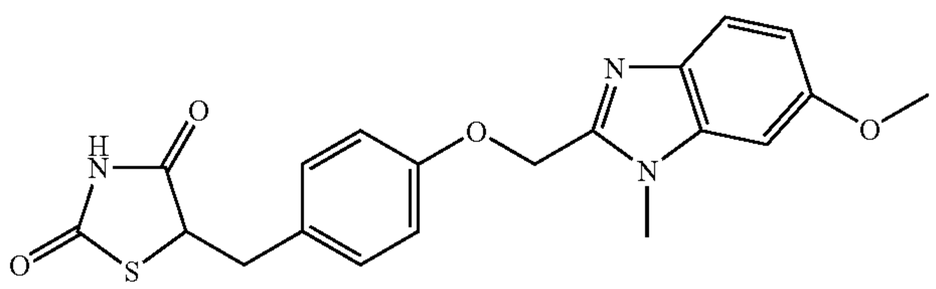
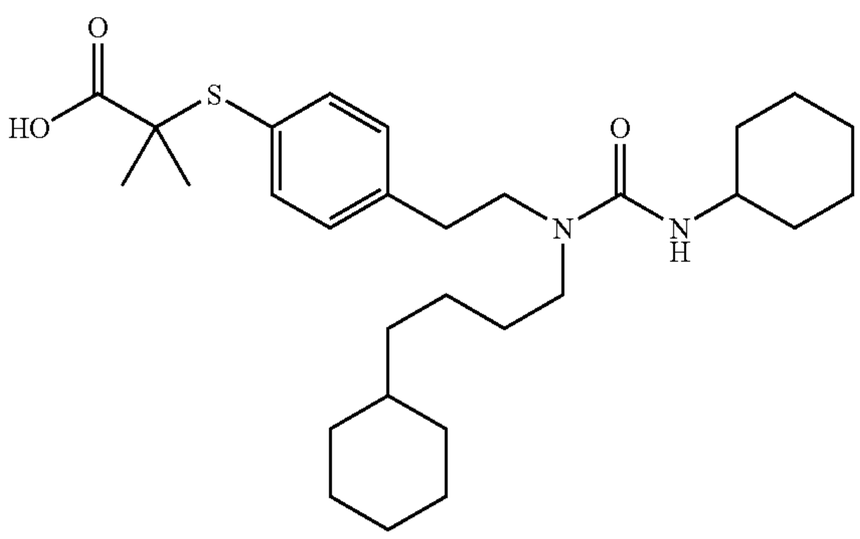


CS-011
Rivoglitazone



GW-9578

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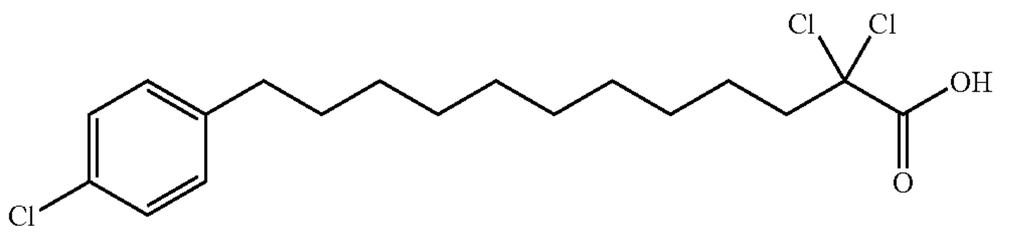

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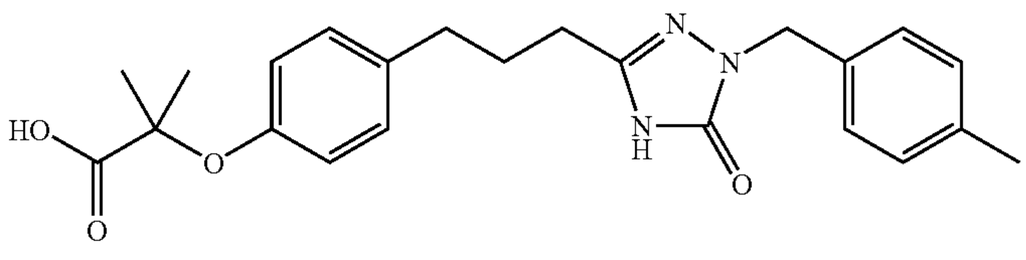

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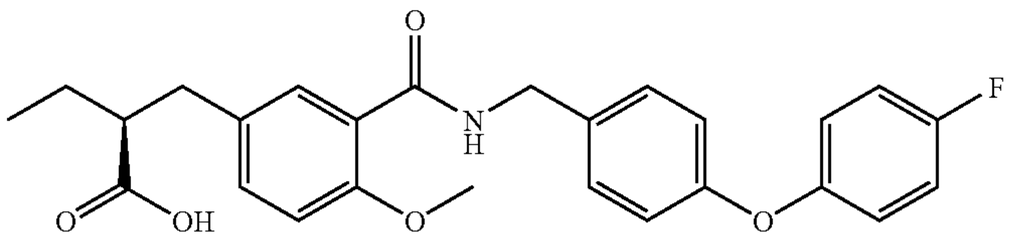
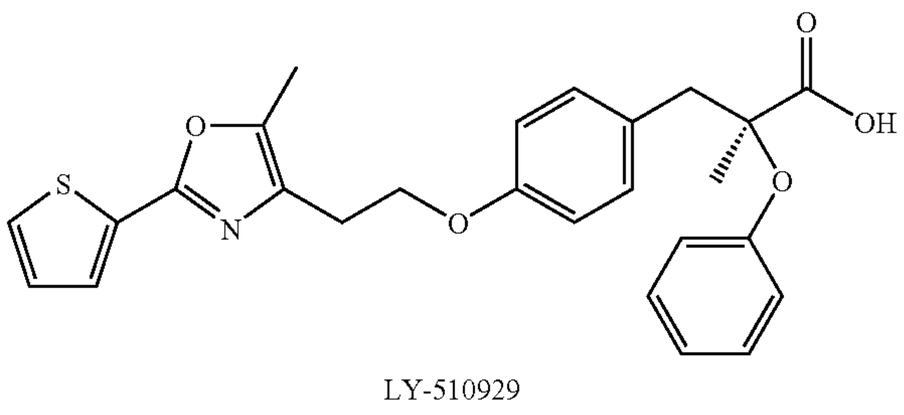


KRP-101



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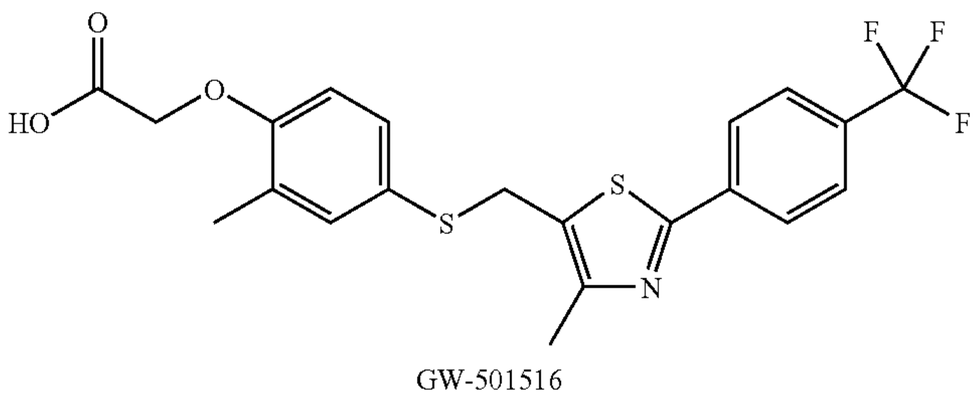

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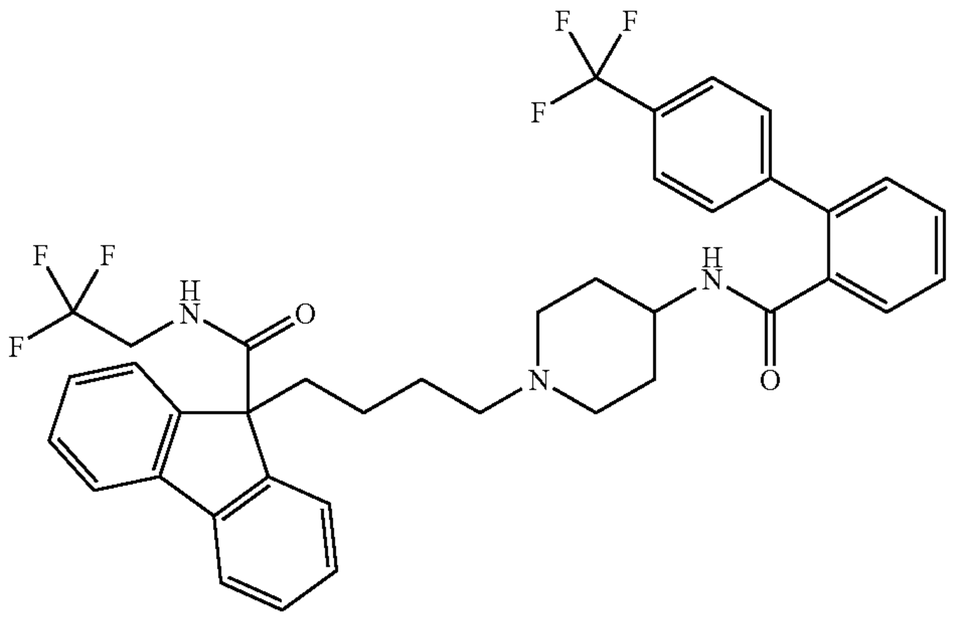

BMS-201038

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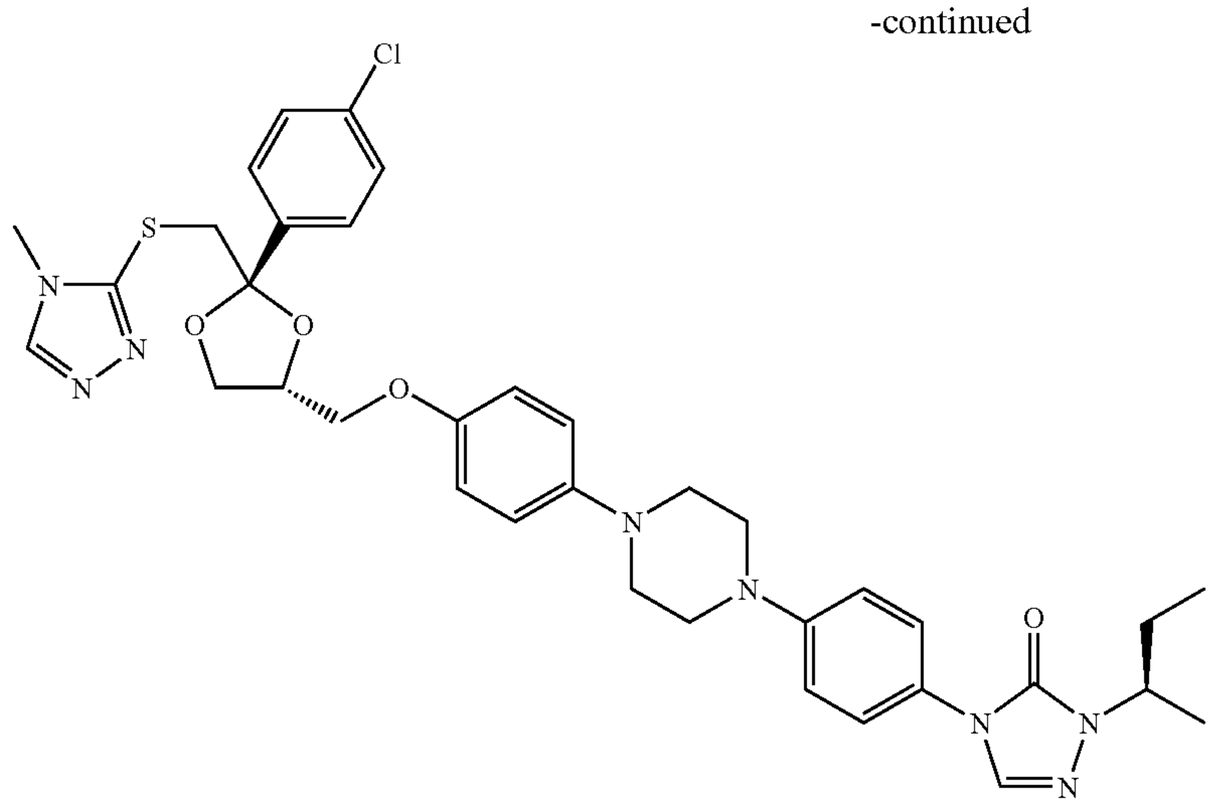

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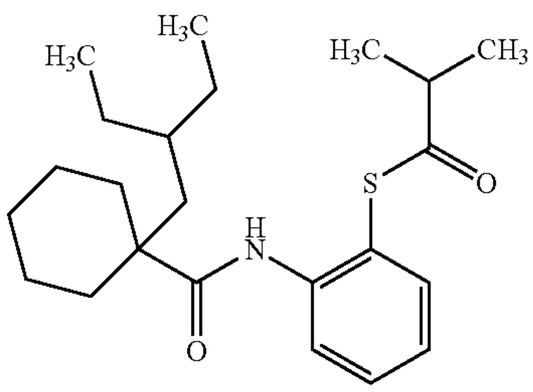

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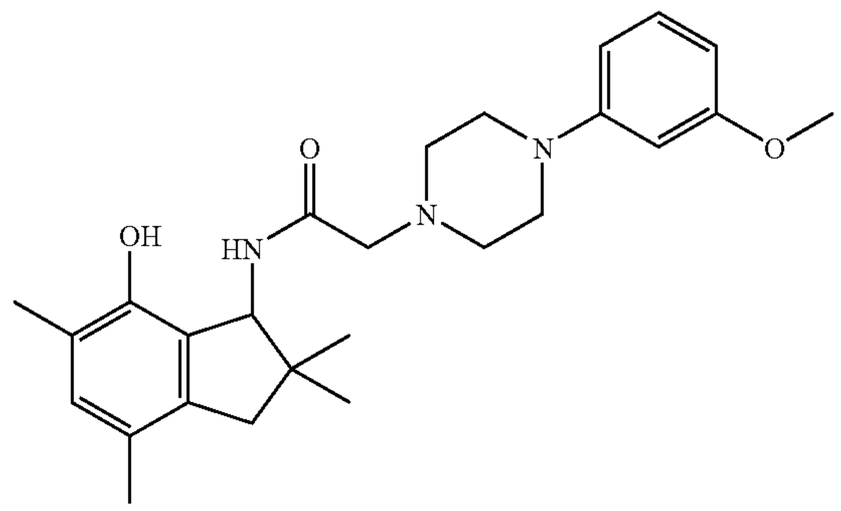

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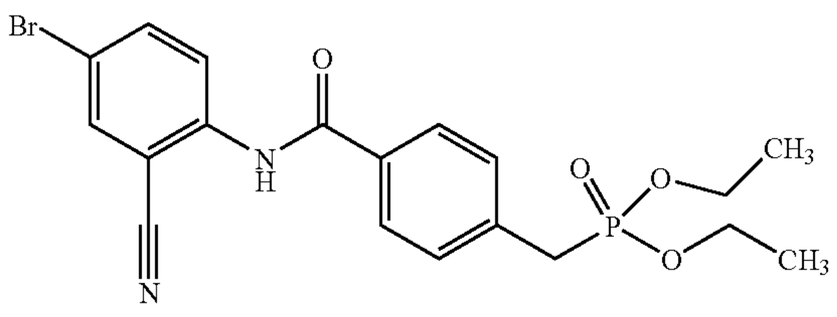

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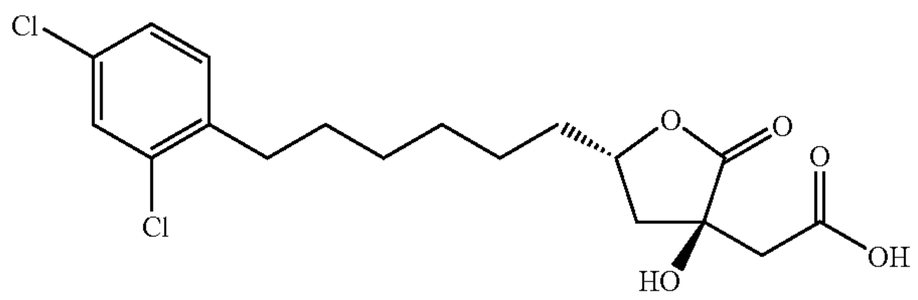

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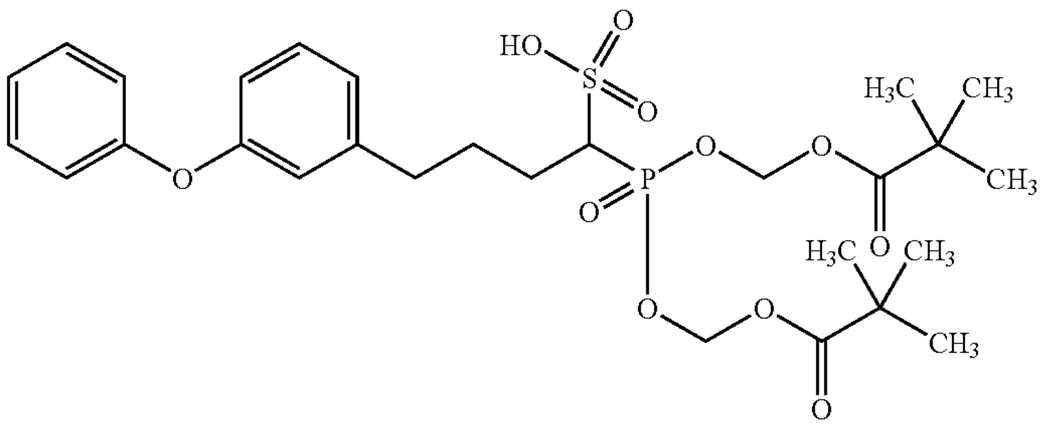

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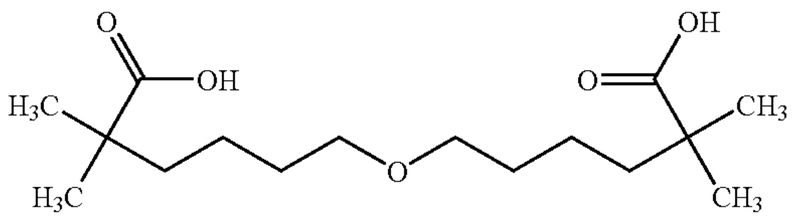

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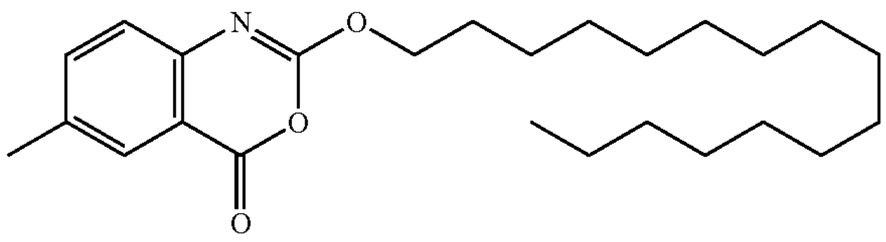

ATL-962

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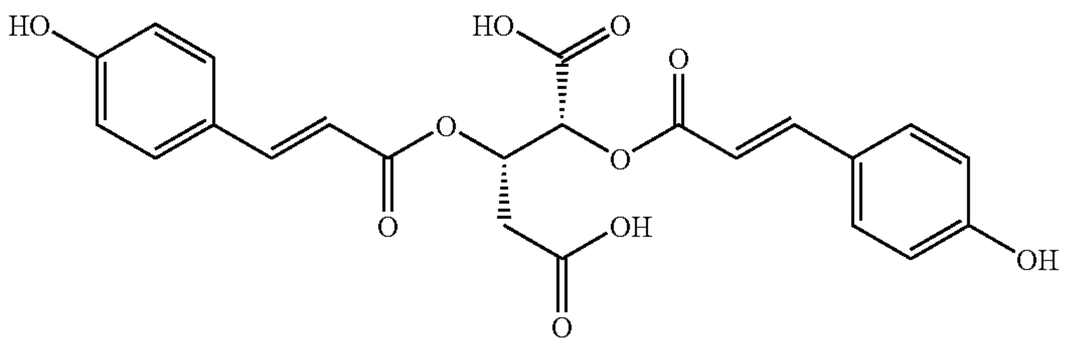

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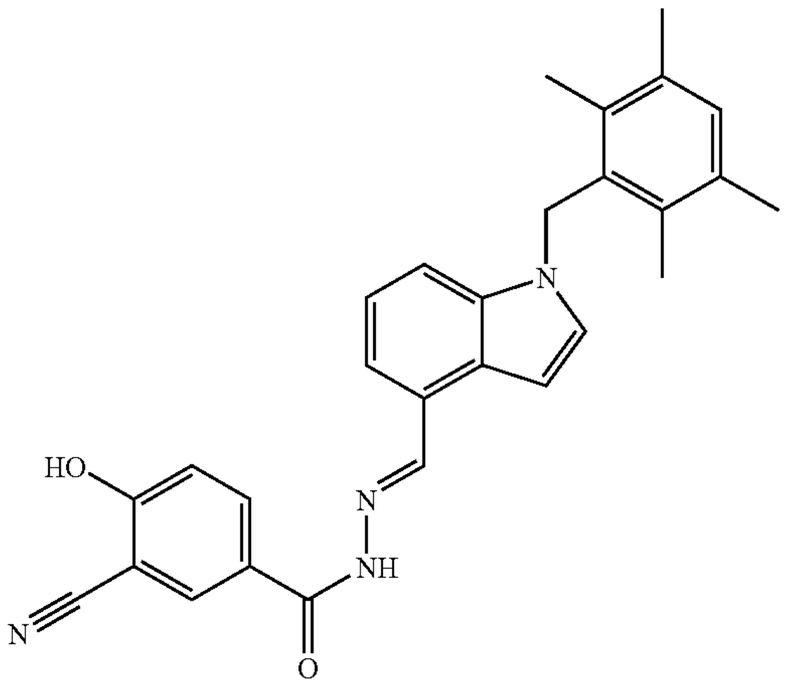

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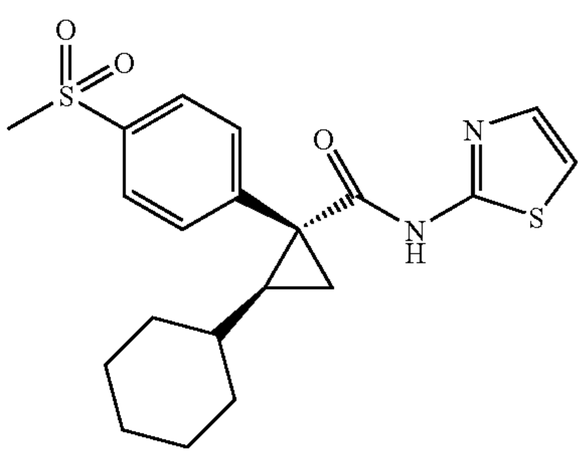

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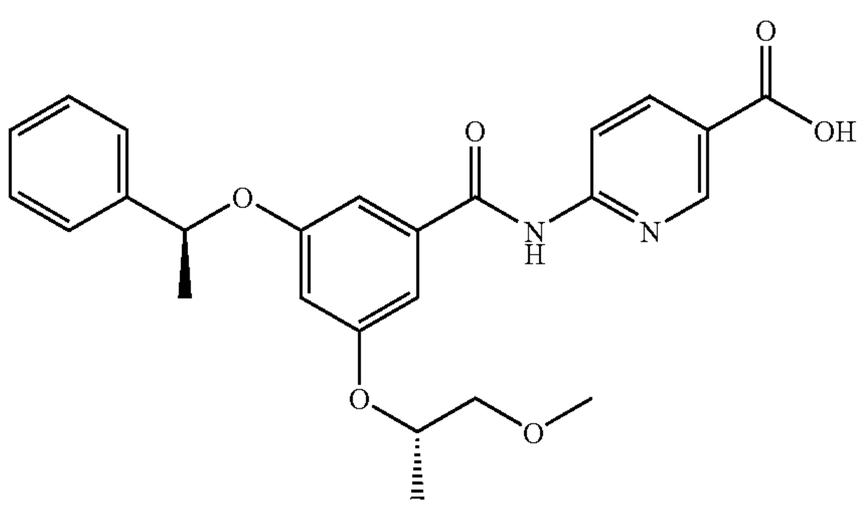
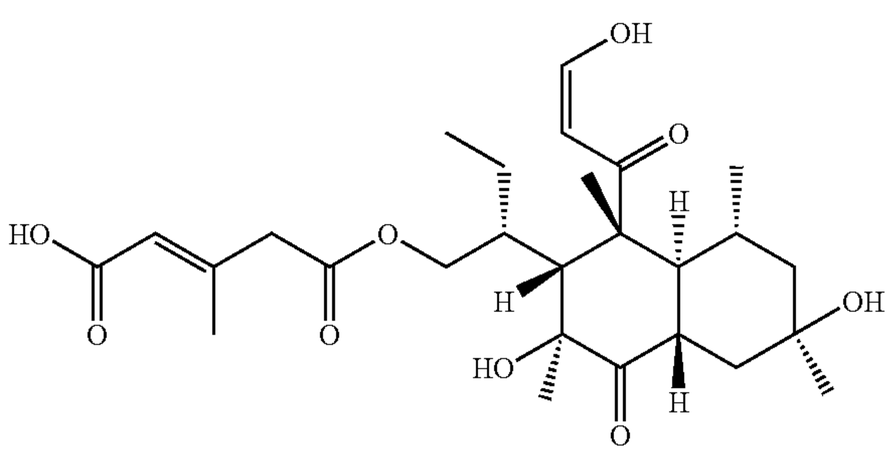


GKA-50



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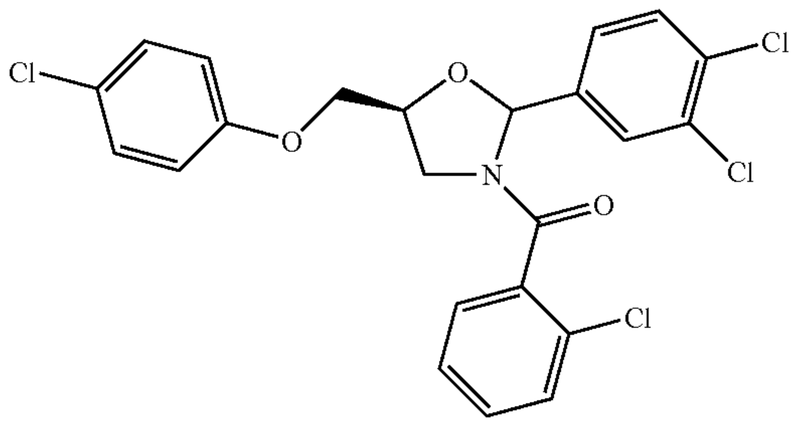
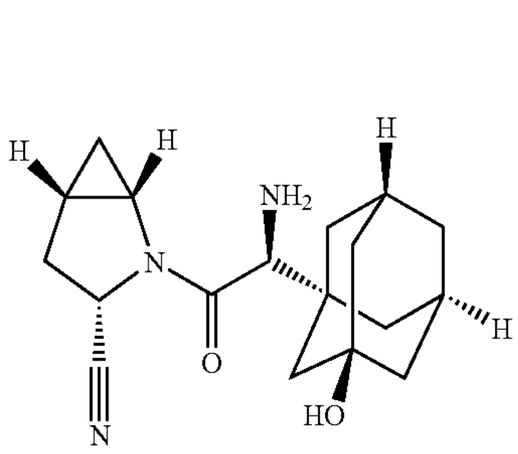


KST-48



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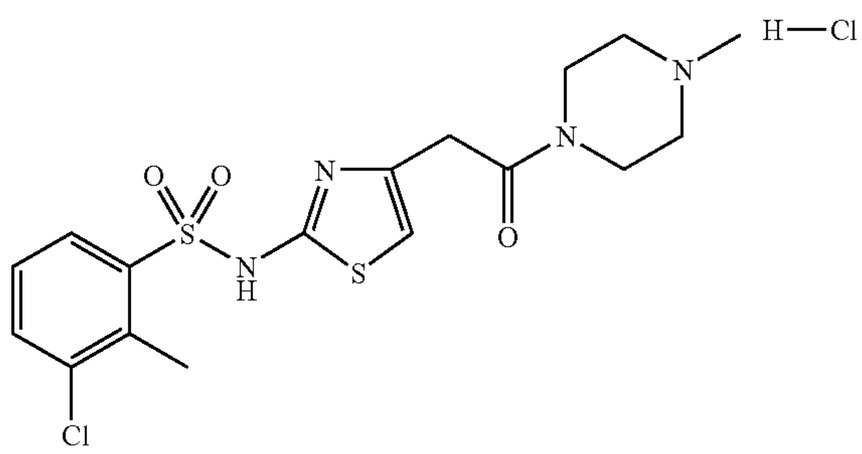

BVT-2733

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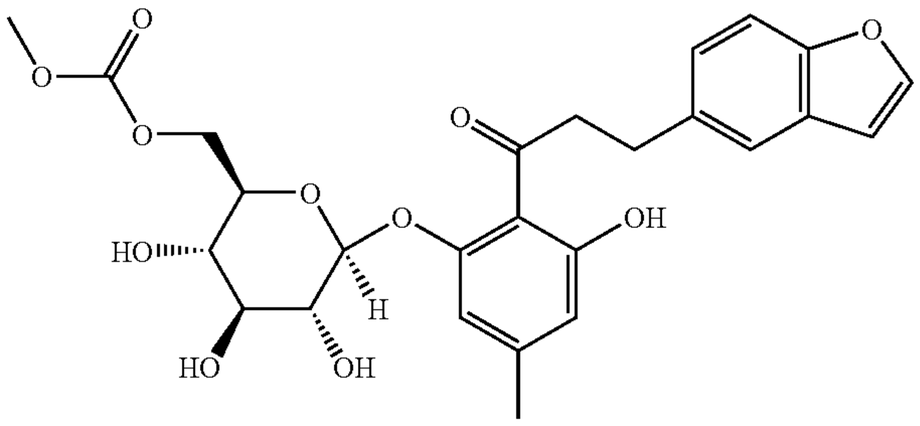

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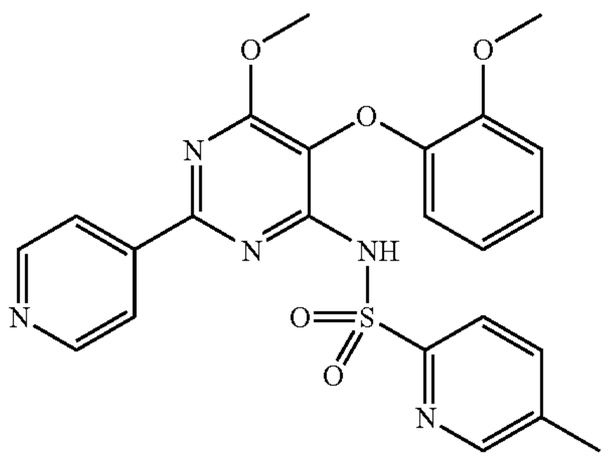
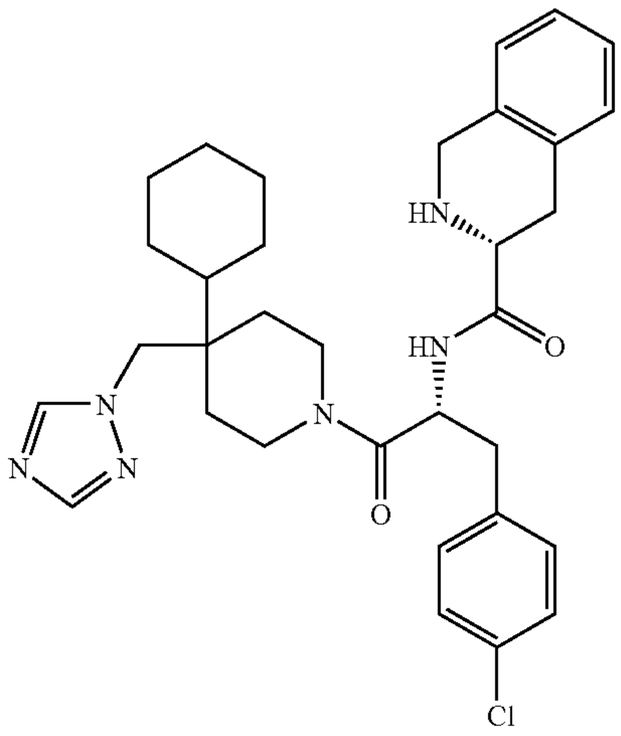


SPP-301



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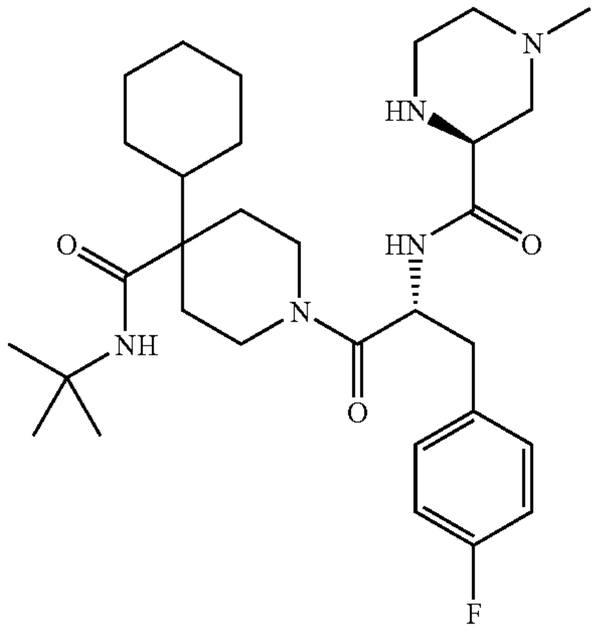
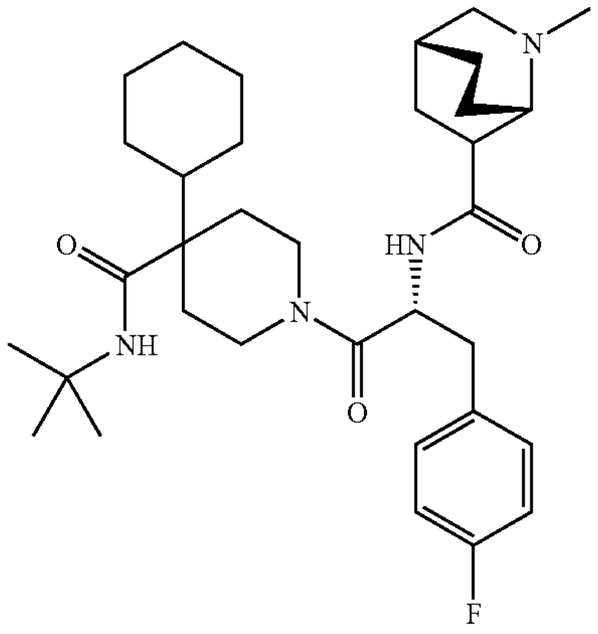
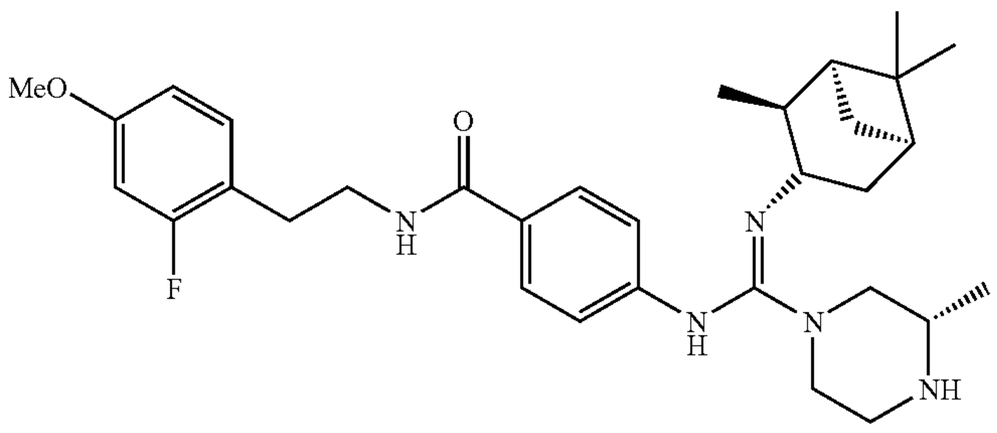


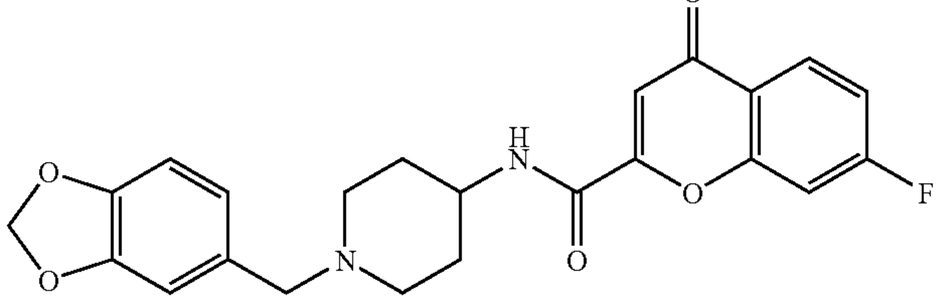
MB243



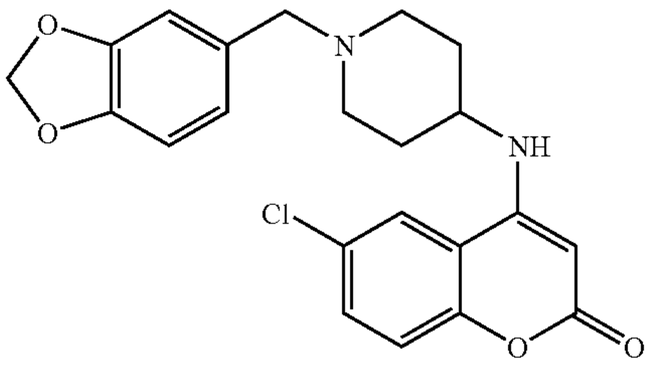
RY764



CHIR-785



A-761



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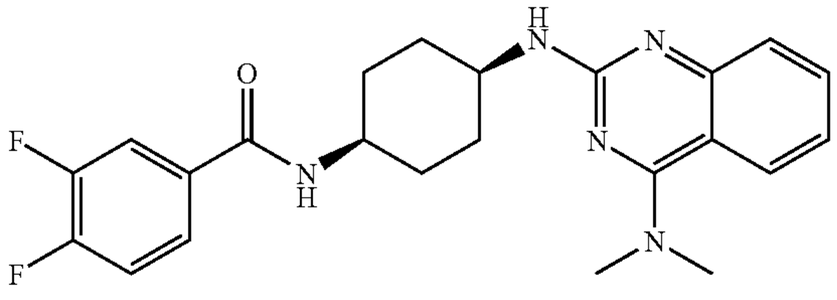

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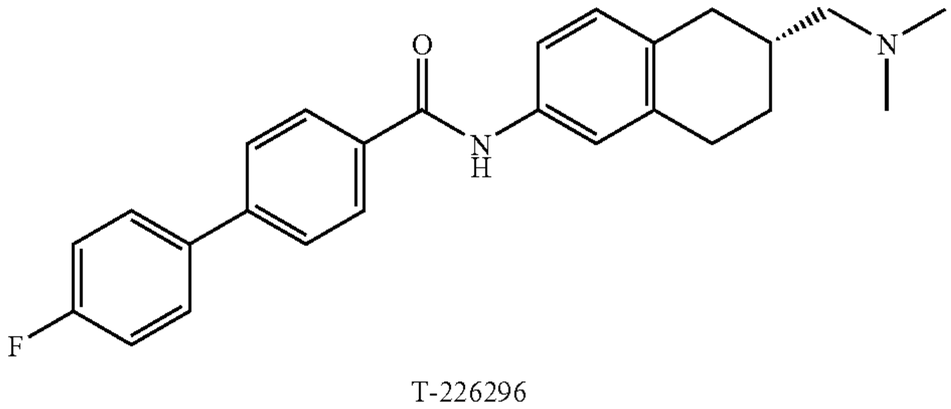

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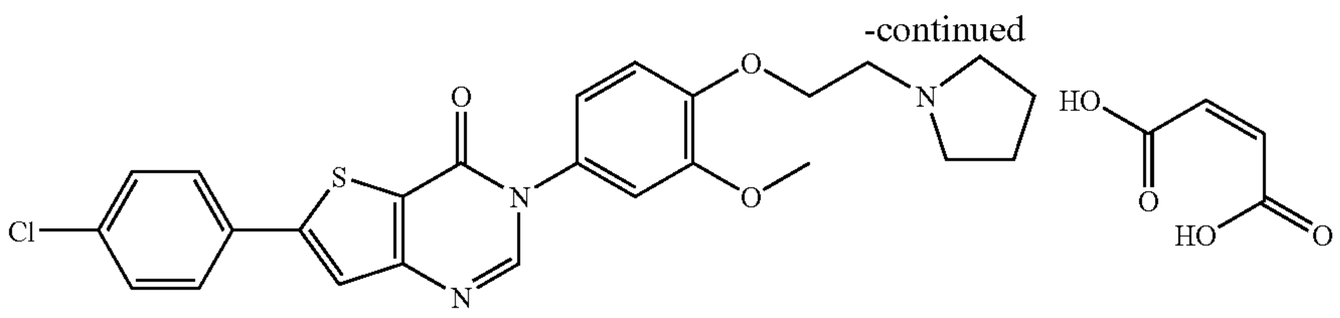

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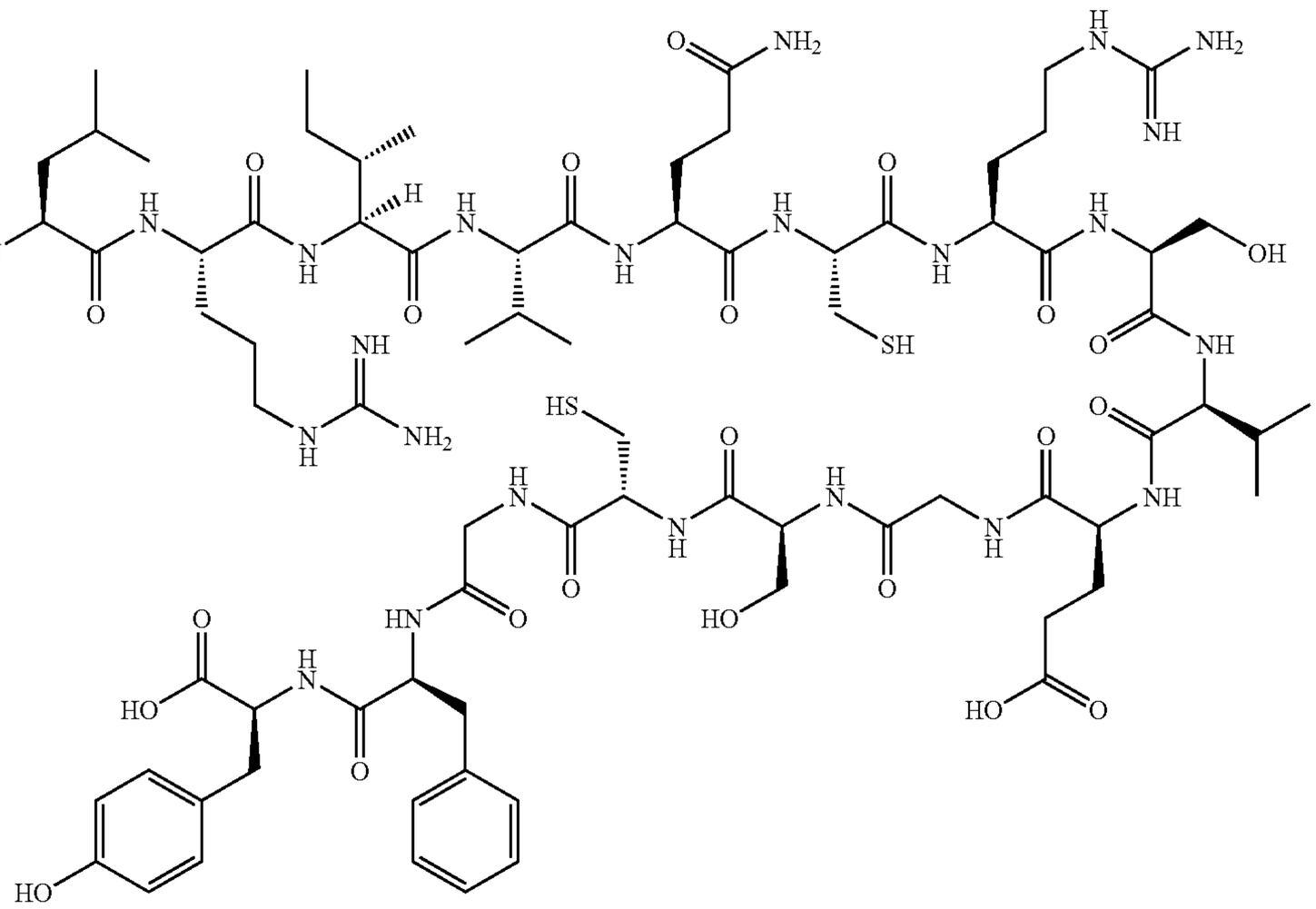

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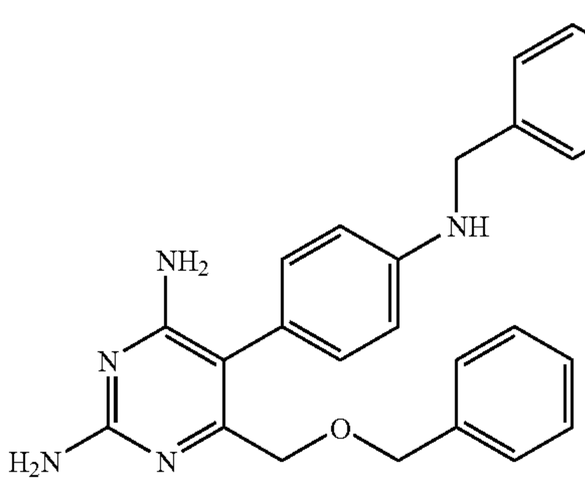

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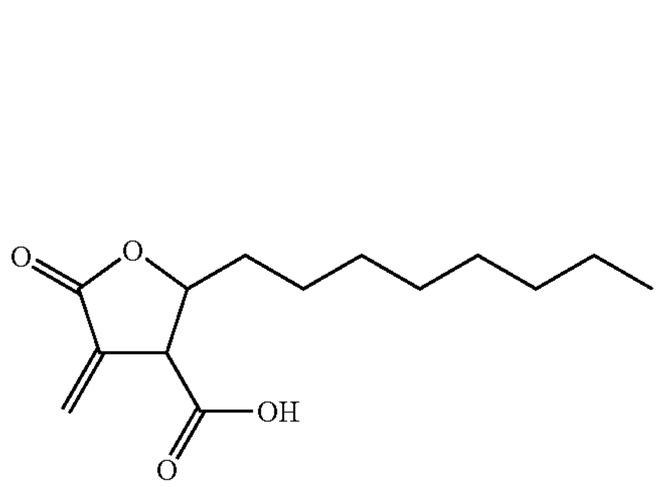

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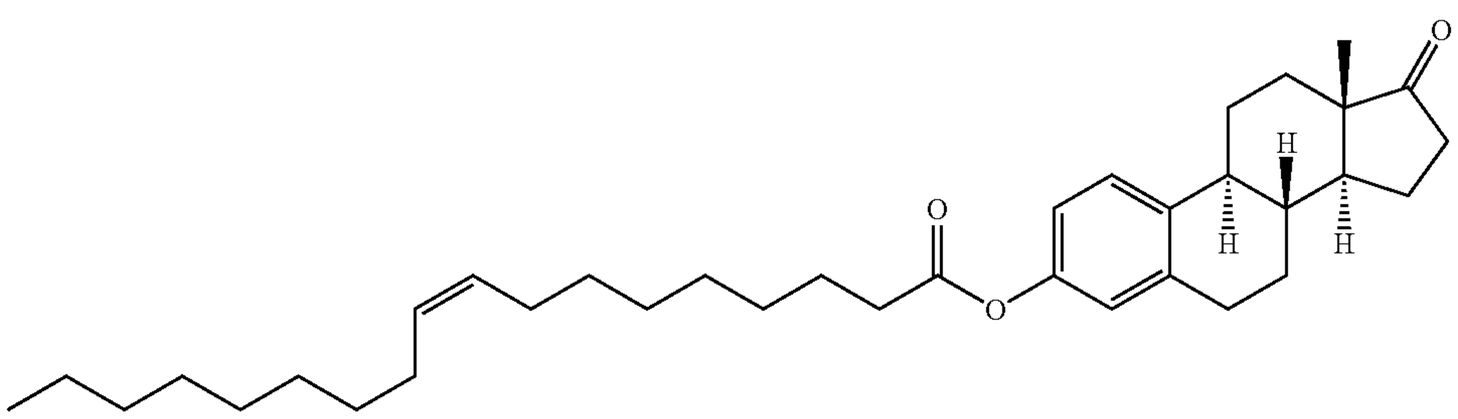

oleoyl-estrone

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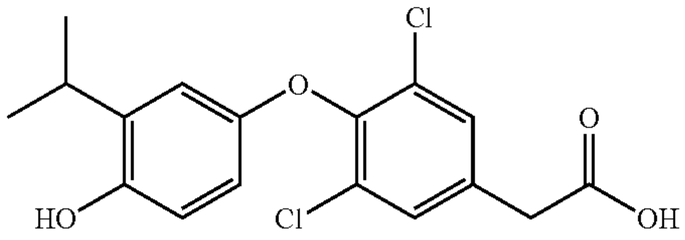

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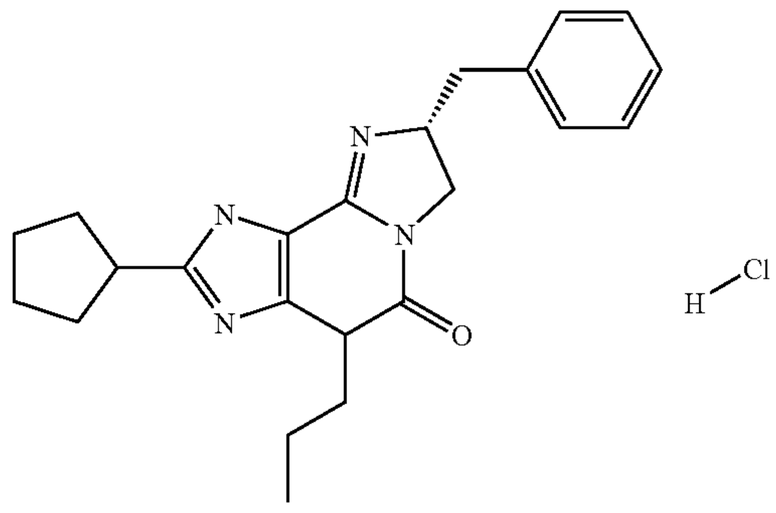
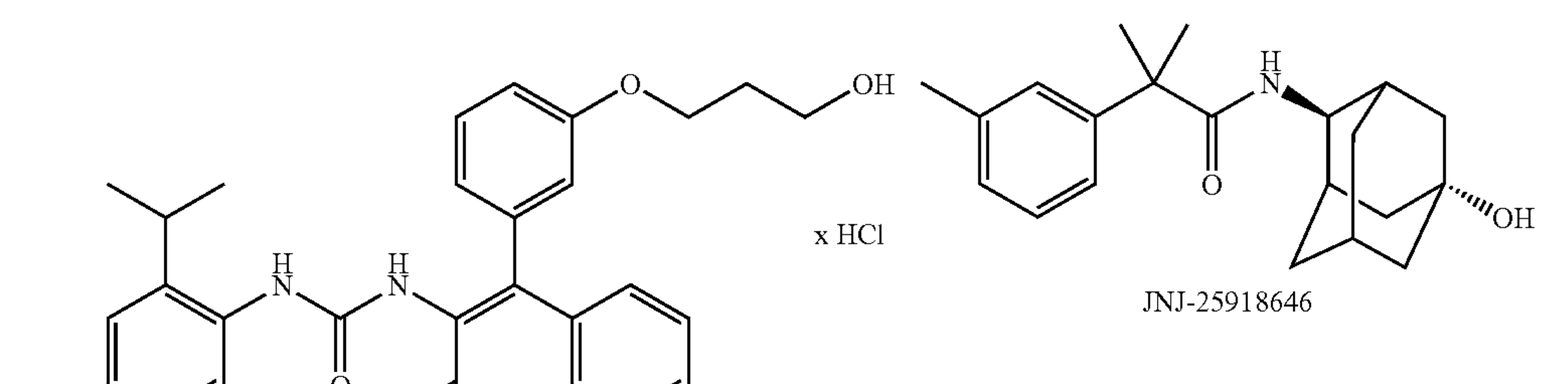


KCP-265



SMP-797

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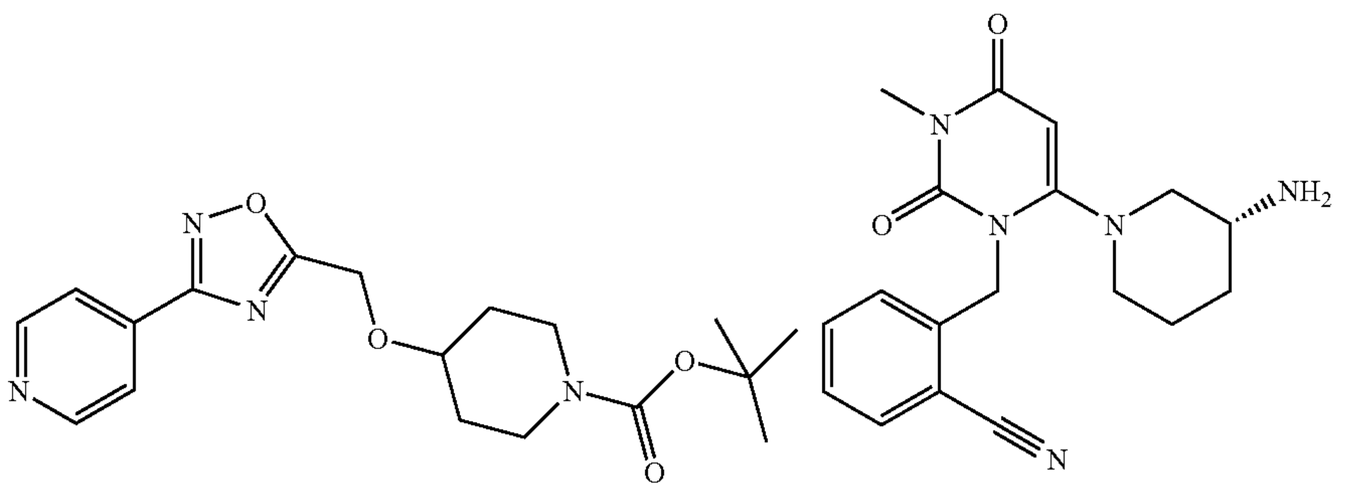

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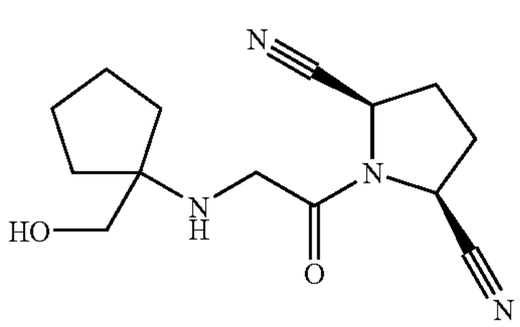
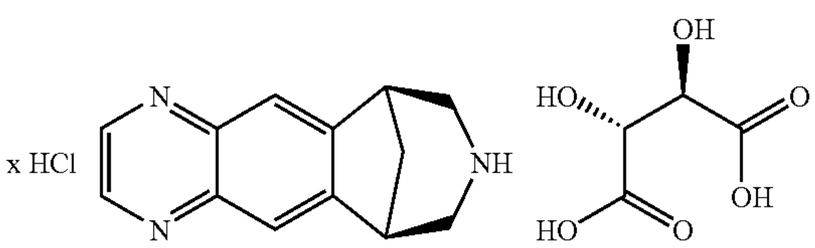
SYR-322



DP-893



Varenicline Tartrat

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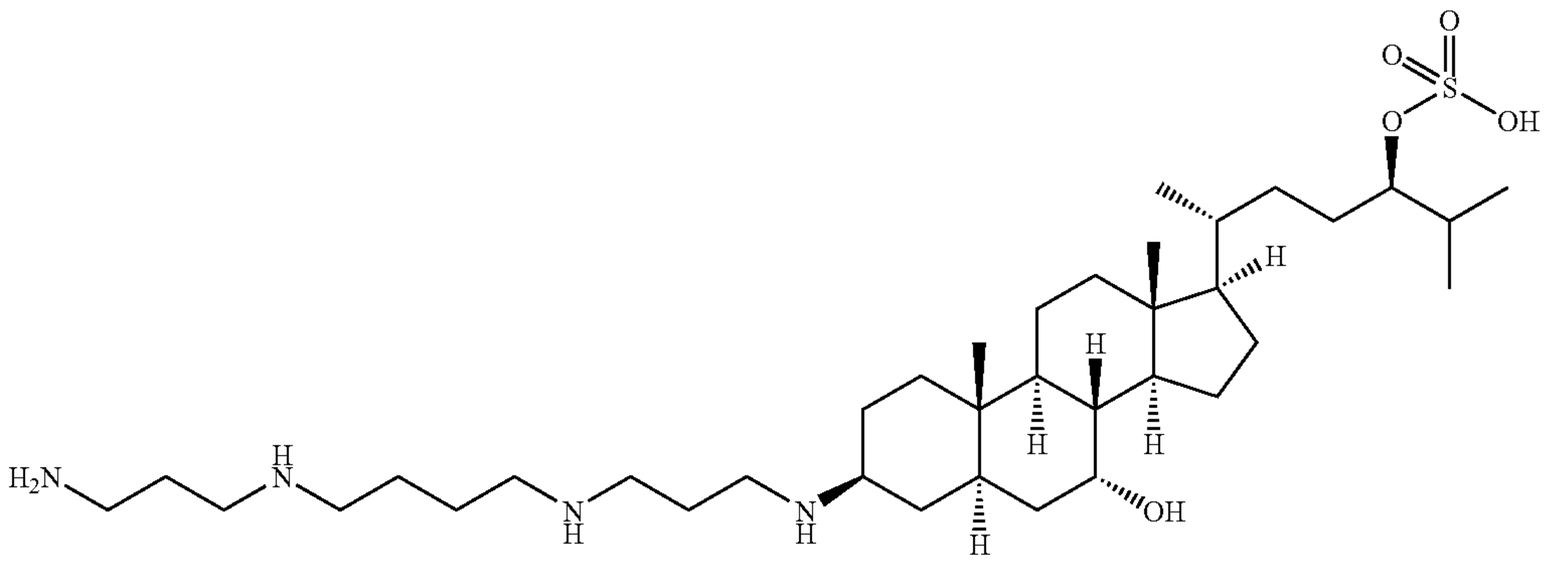
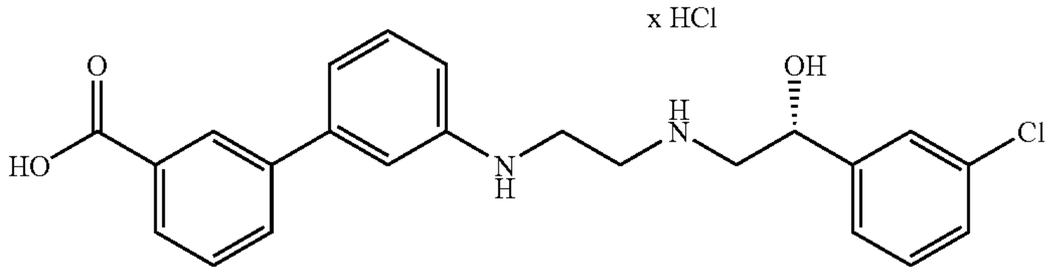
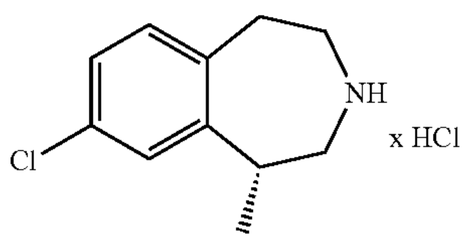


trodusquemine

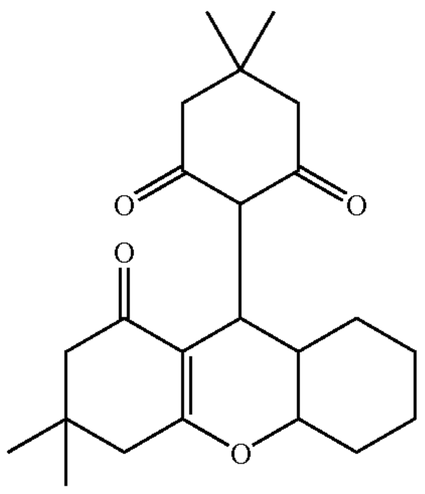
x HCl



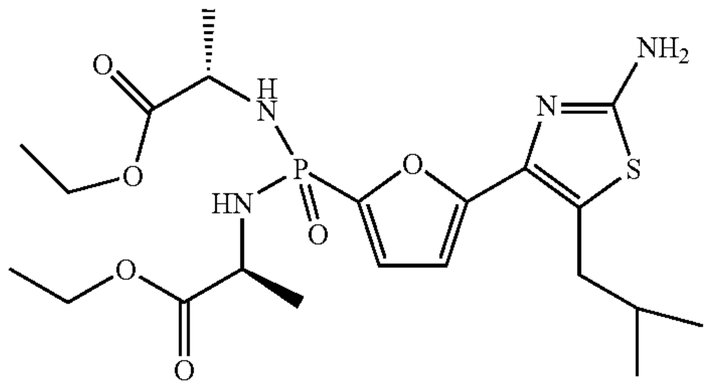
Solabegron



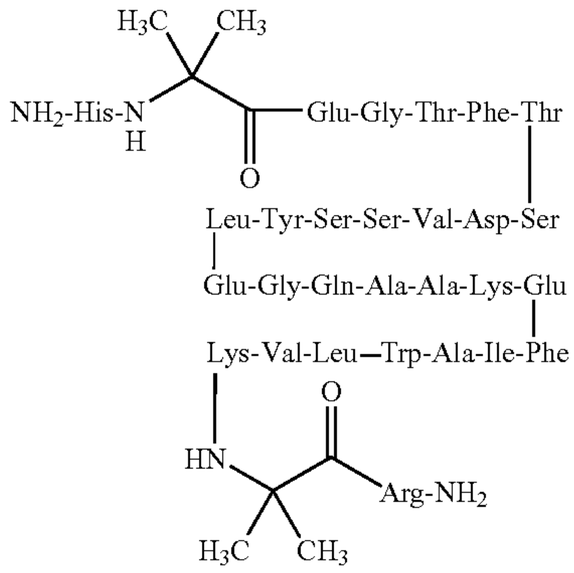
Lorcaserin Hydrochlorid

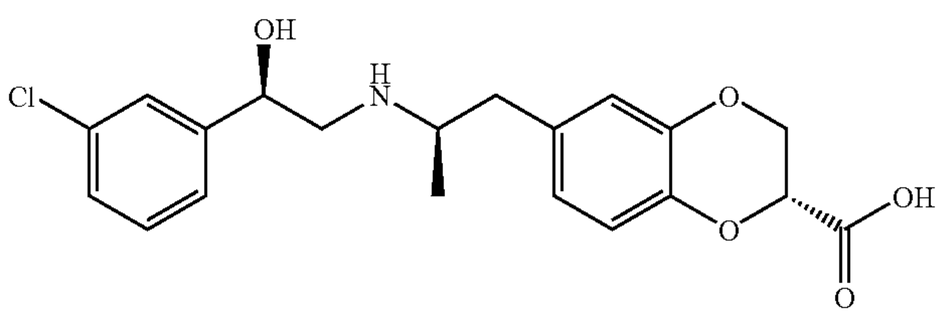


L-152804



MB-06322
CS-917





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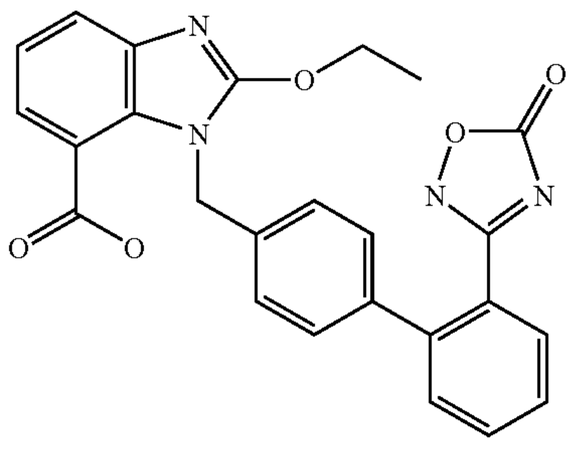
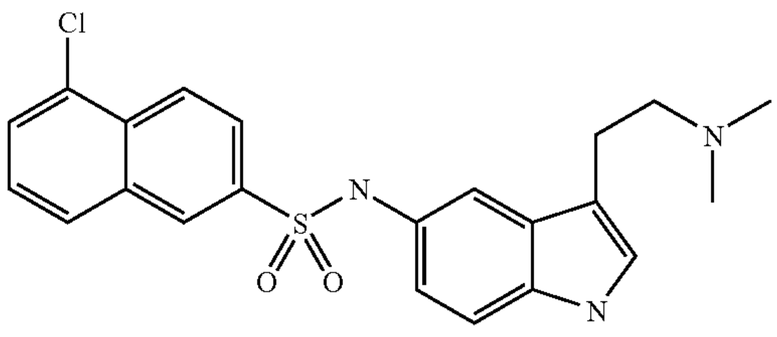
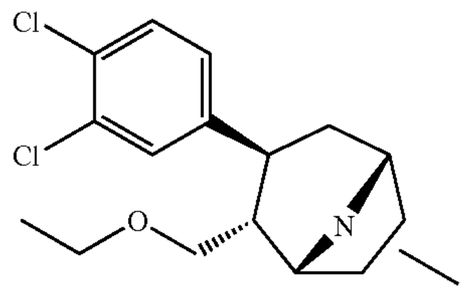


TAK-536



E-6837



tesofensine

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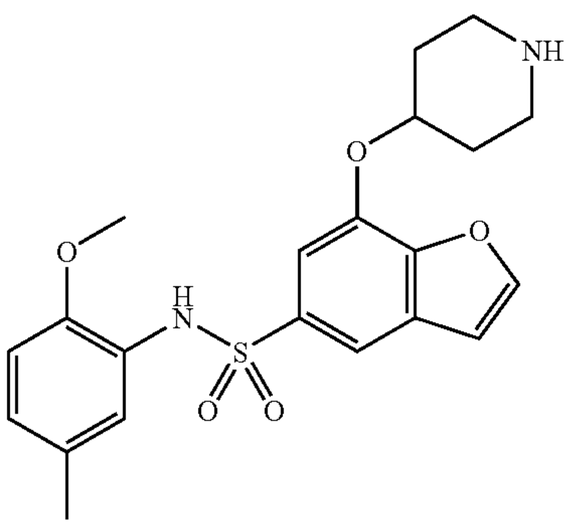
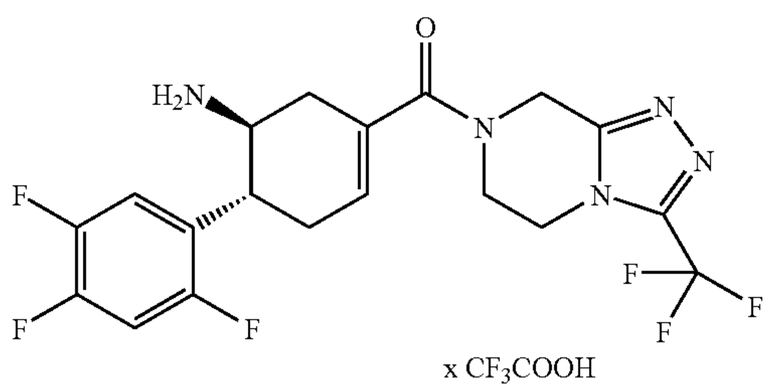
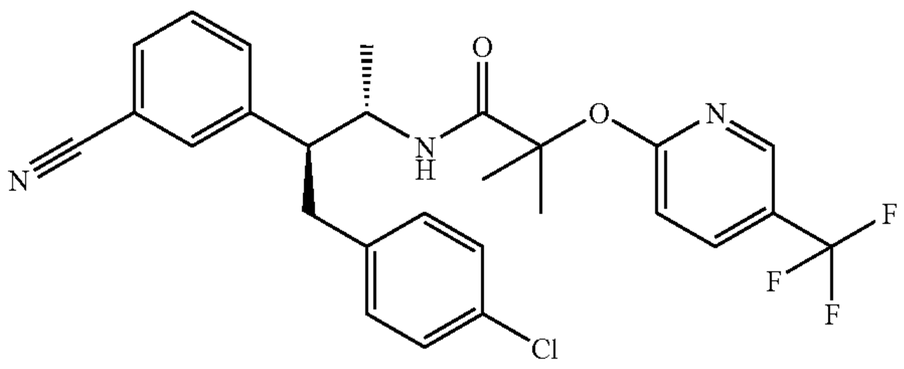


BVT-74316

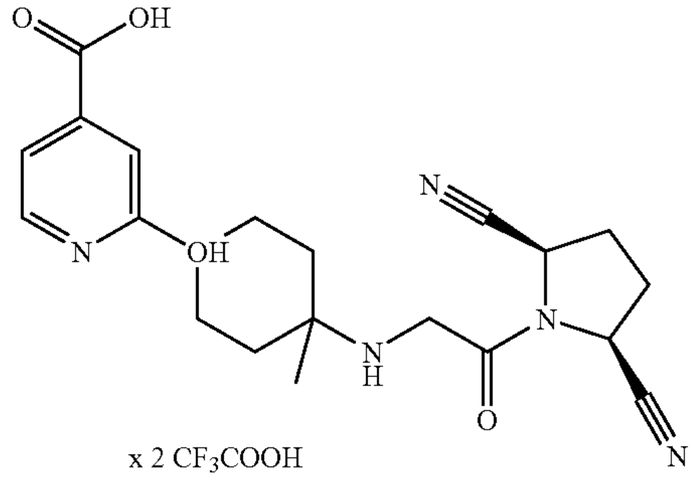


x CF_3COOH

ABT-341

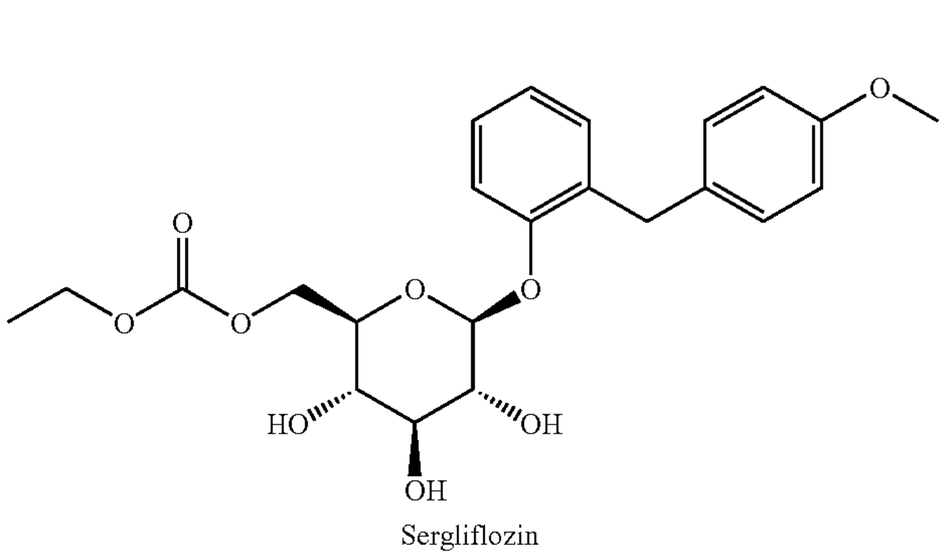


MK-0364



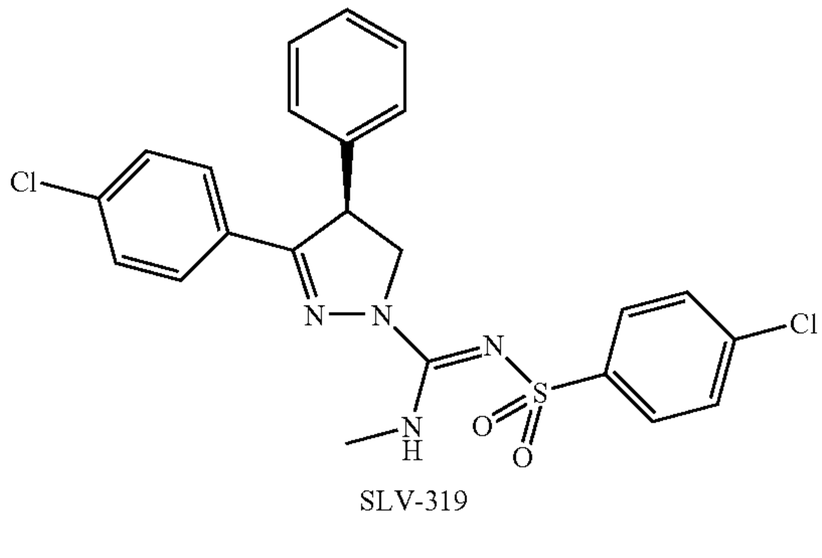
x 2 CF_3COOH

ABT-279

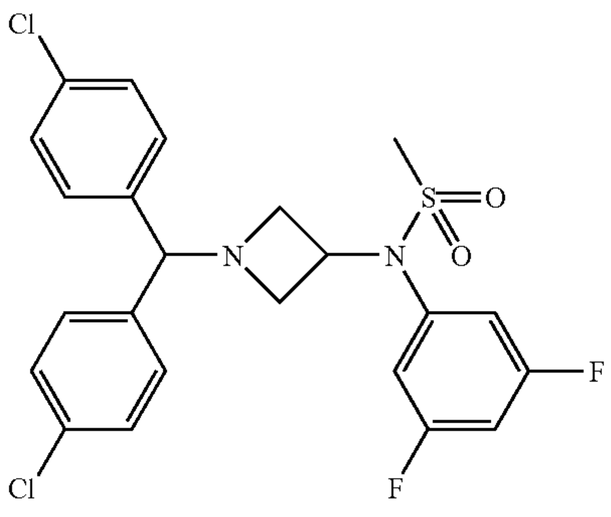


OH

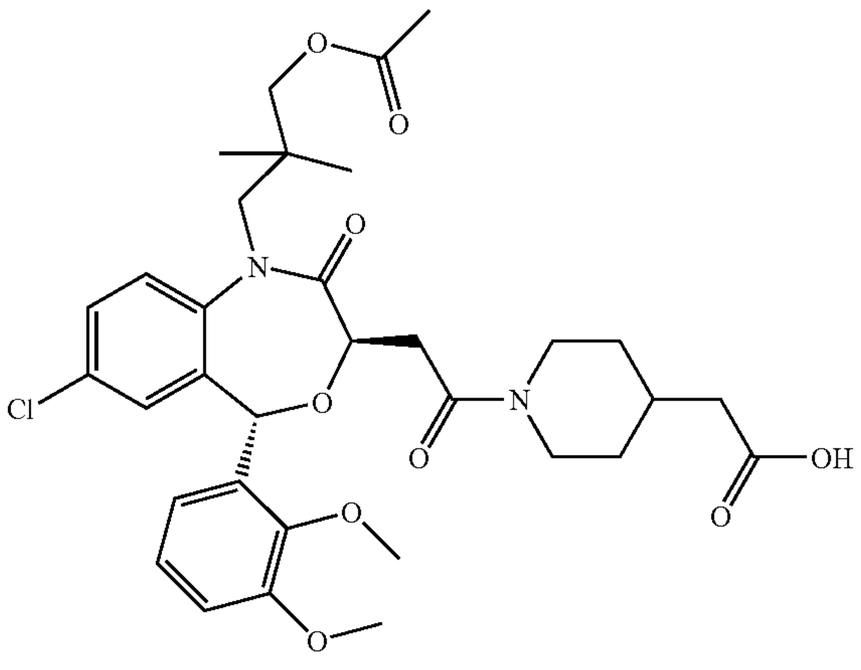
Sergliflozin



SLV-319



AVE 1625



TAK-475 (lapaquistat acetate)

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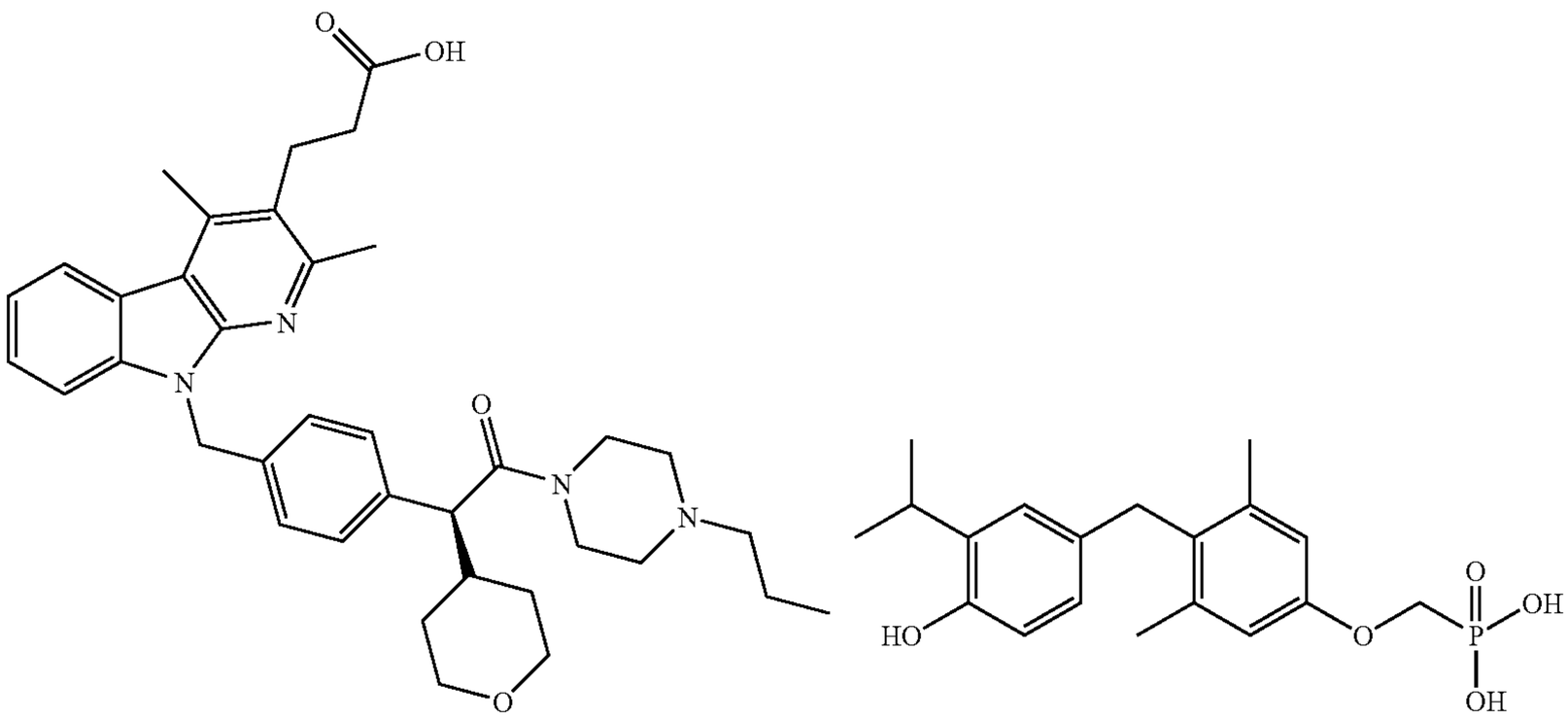
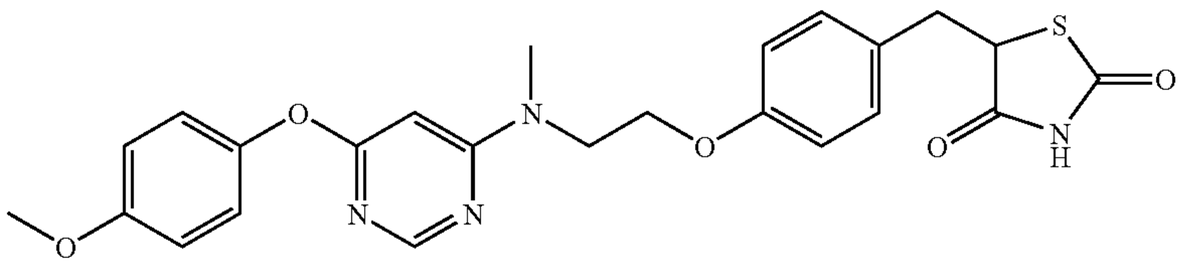


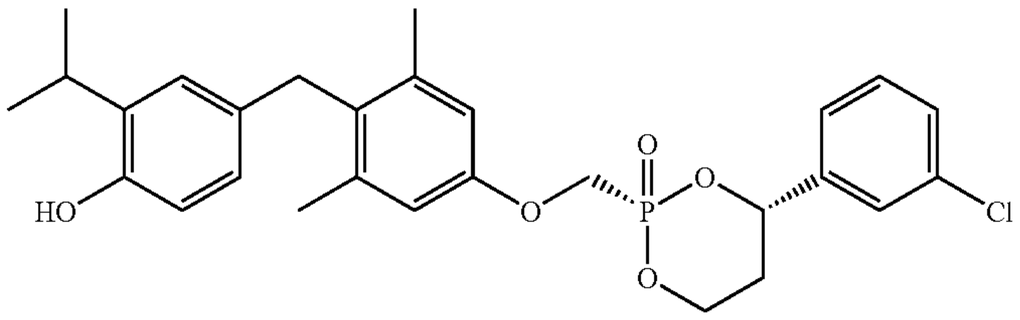
AS-1552133

MB-07344

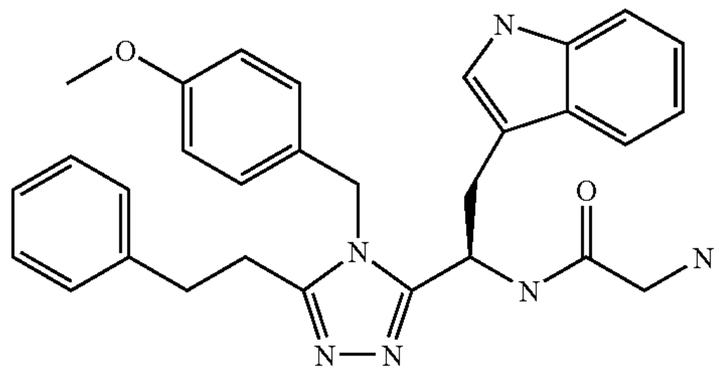


x H_2SO_4

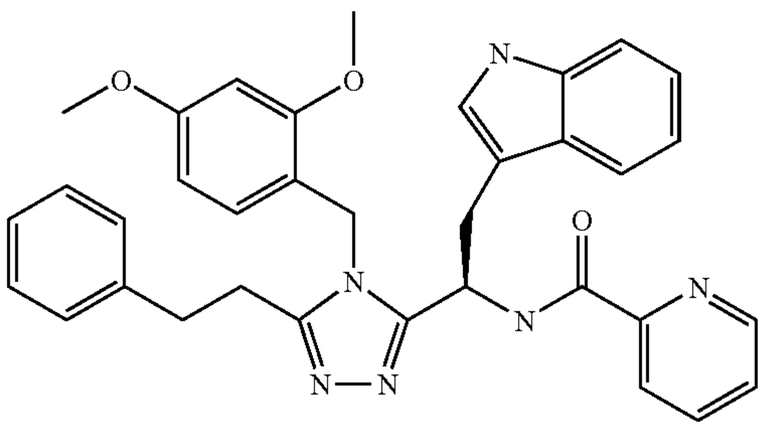
CKD-501 (lobeglitazone sulfate)



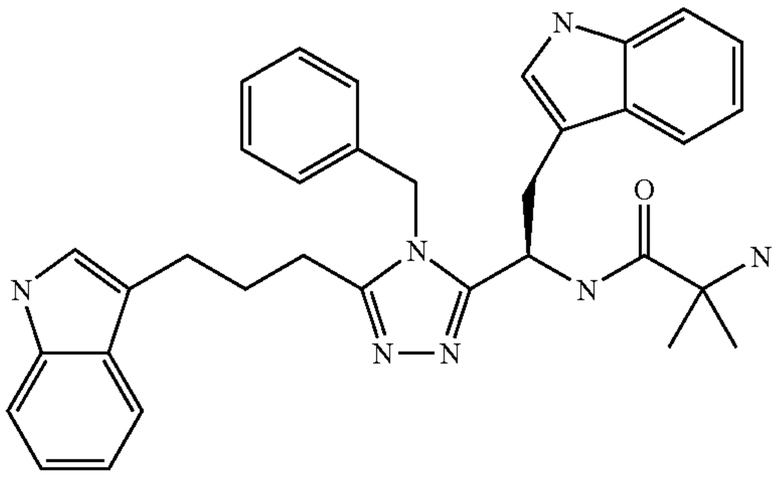
MB-07811



JMV-2959



JMV-3002



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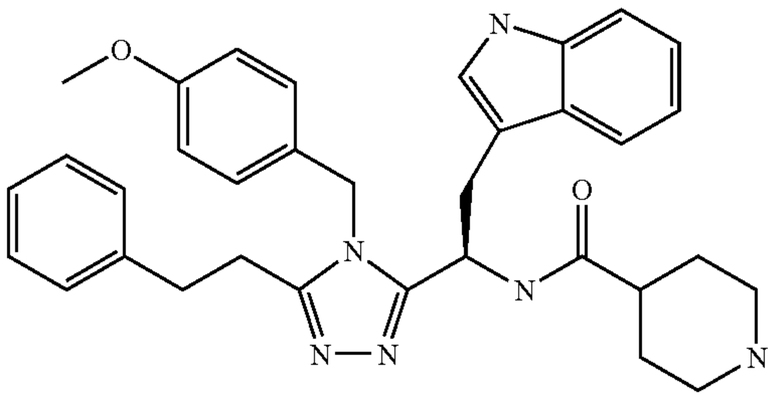

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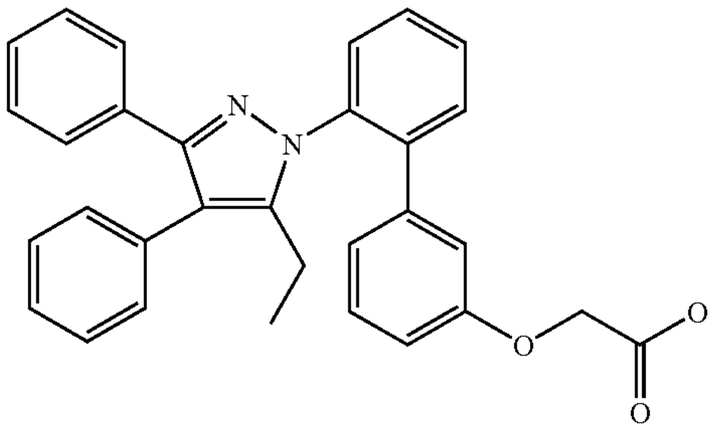

BMS-309403

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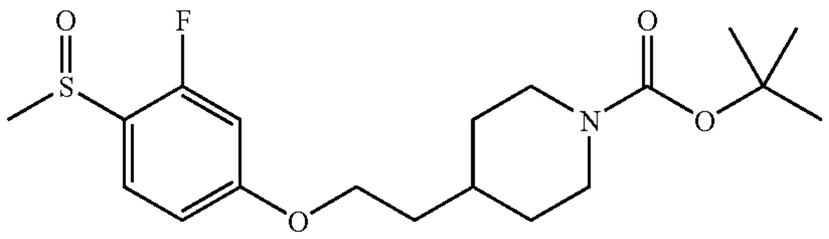
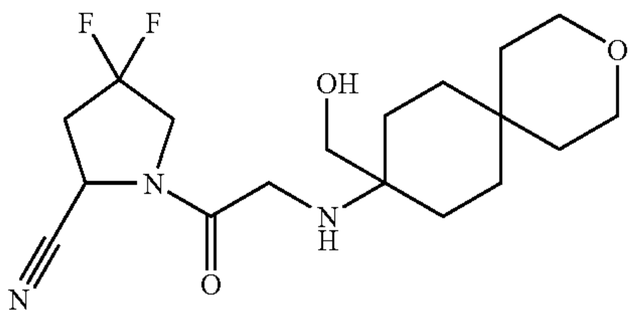
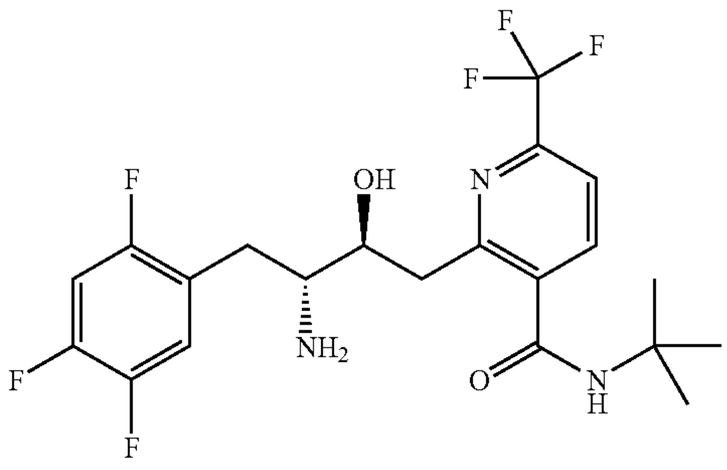


PSN-119-1



S-40755



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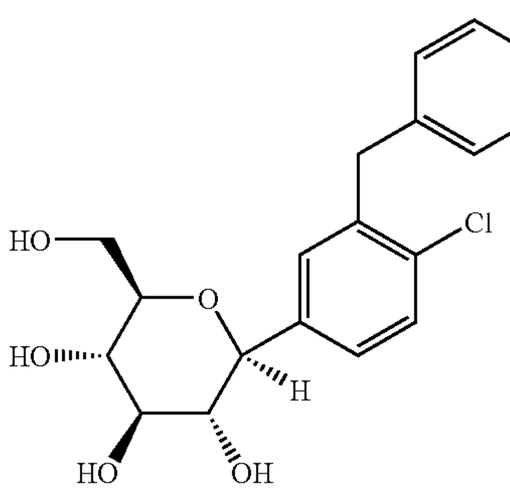
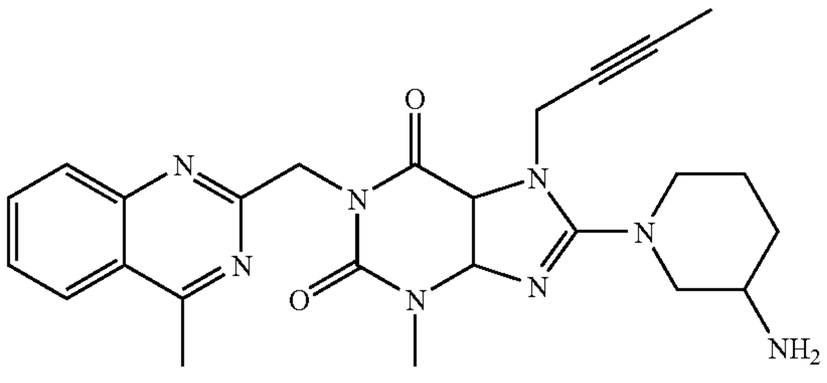
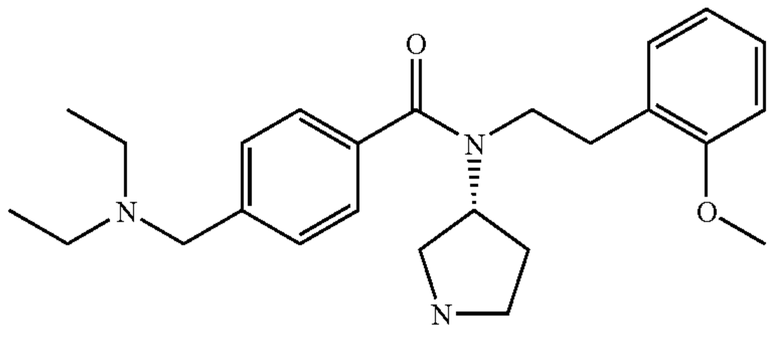


dapagliflozin, BMS-512148



BI-1356



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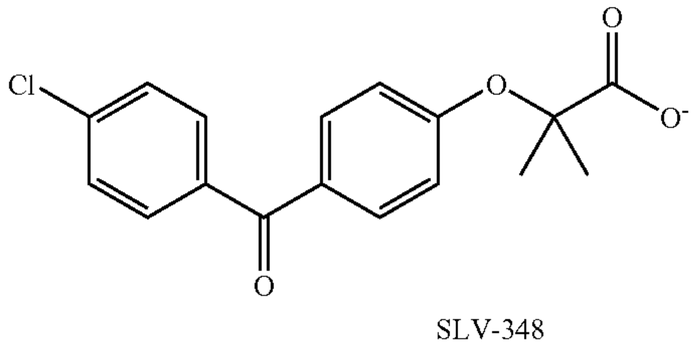
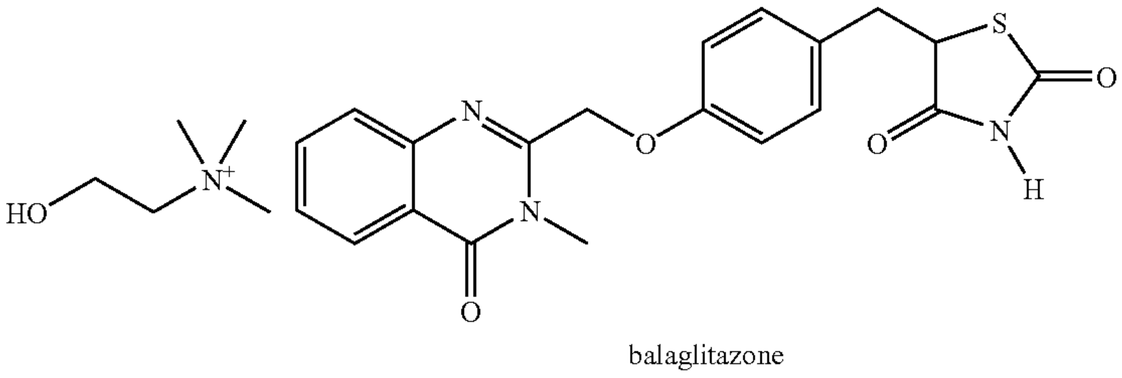


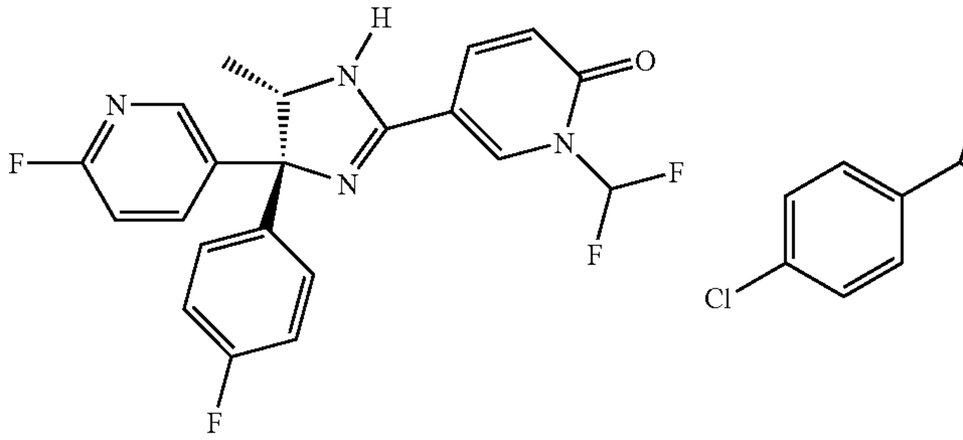
SLV-348



balaglitazone

"NPY-5-BY"

BMS-711939



BMS-687453

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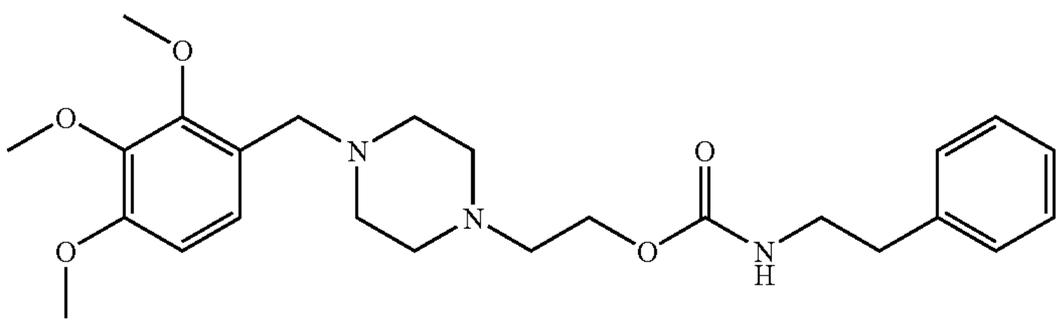
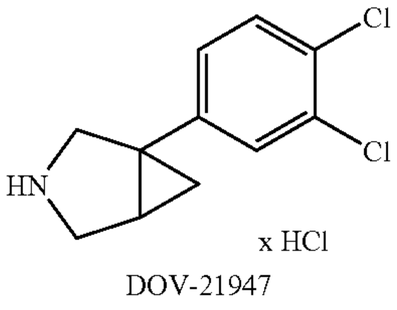


ST-3473



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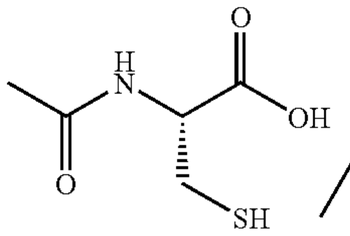
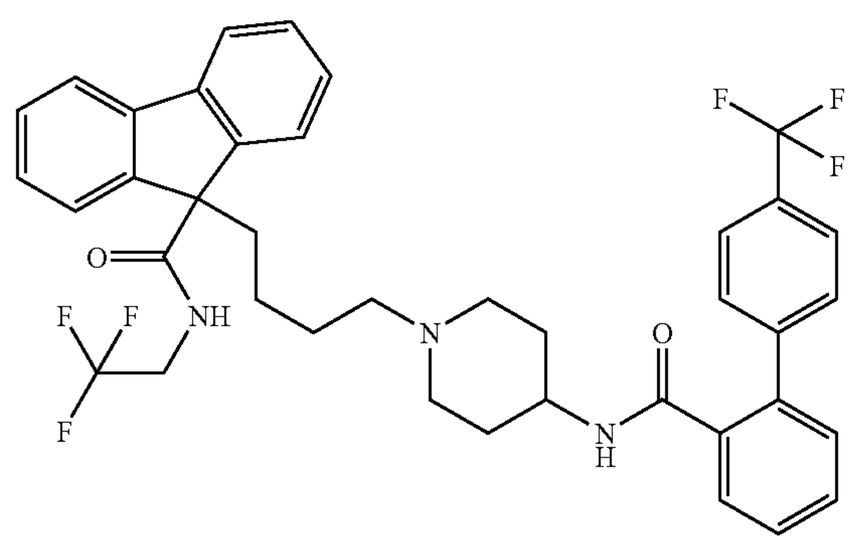
DOV-21947



DM-71



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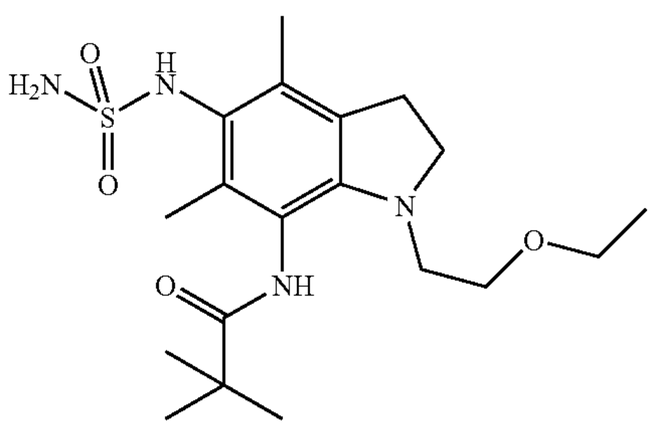

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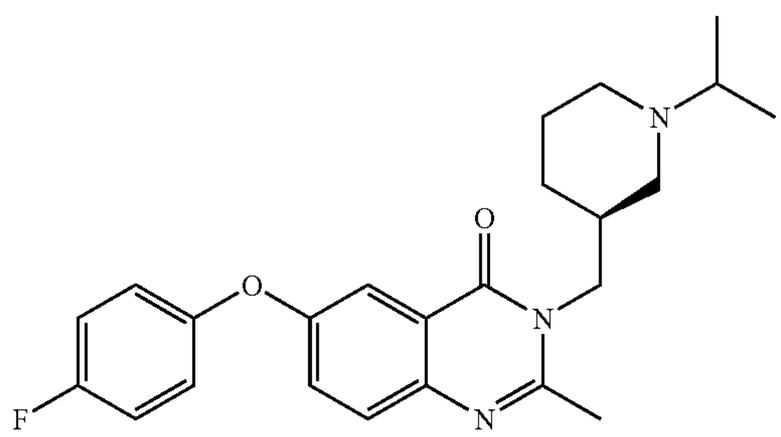

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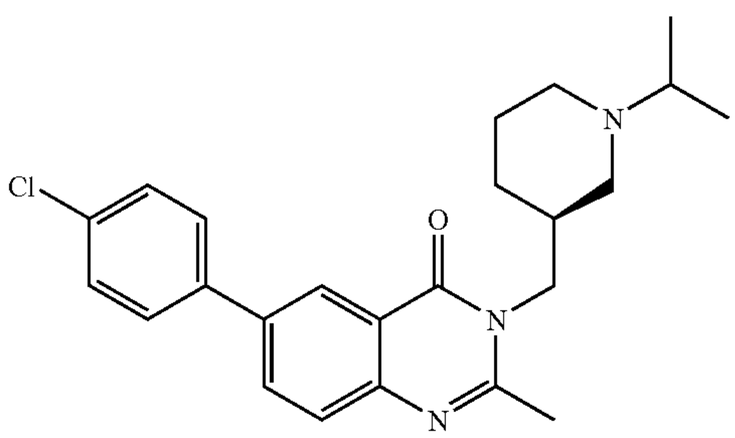

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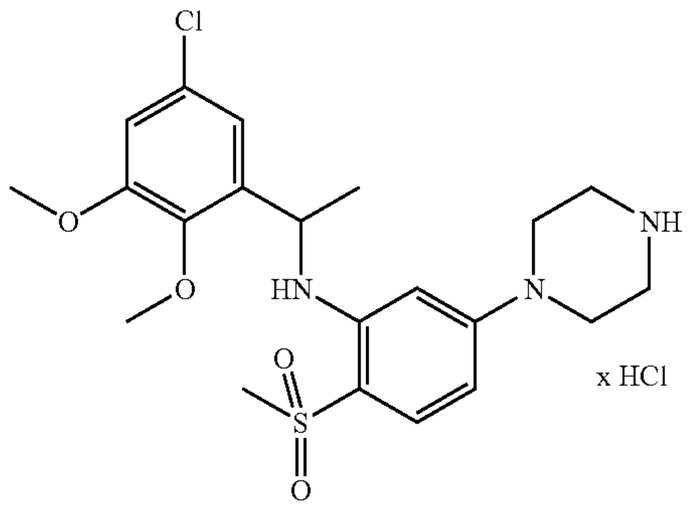

x HCl

PRX-07034

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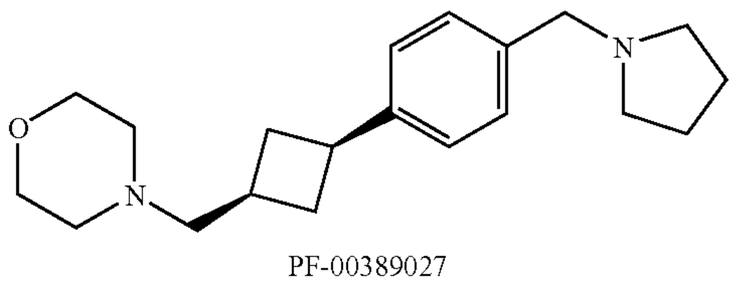

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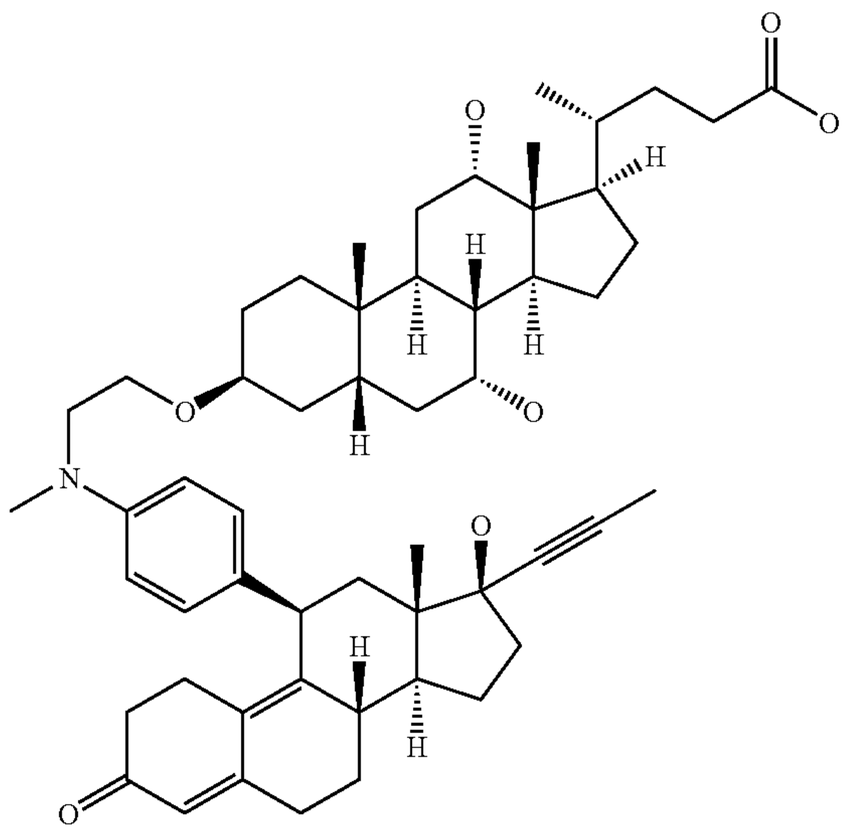

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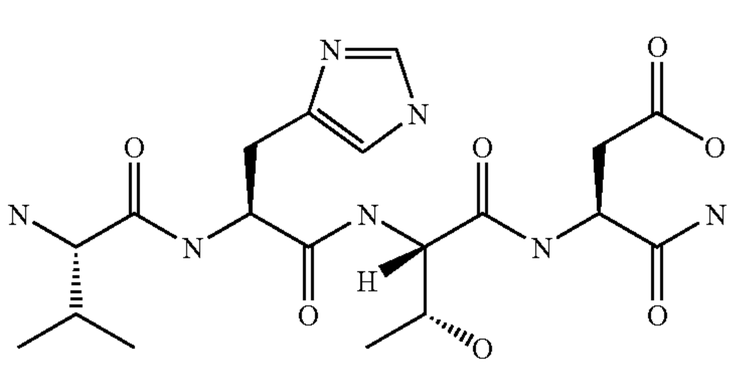

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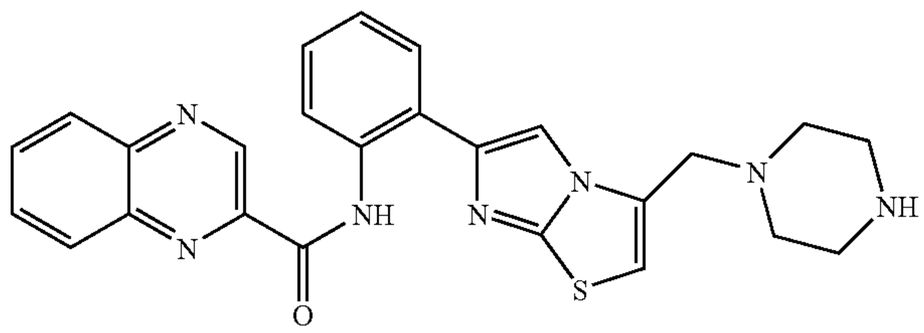

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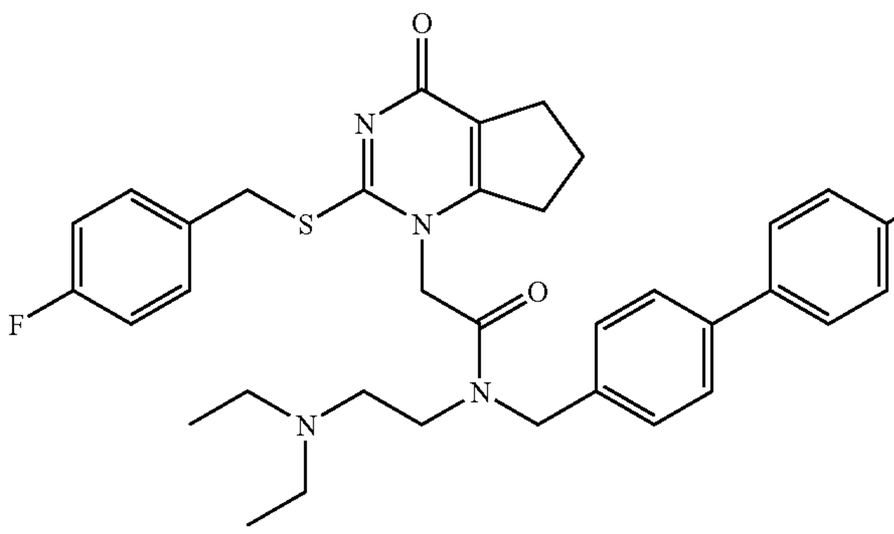

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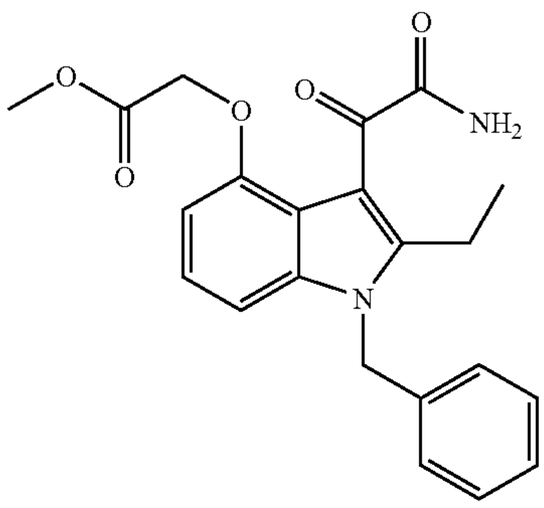

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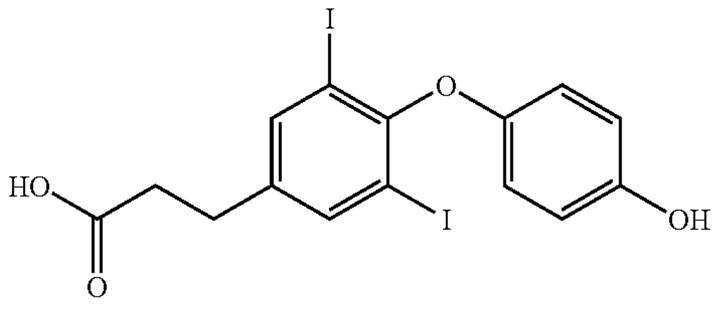

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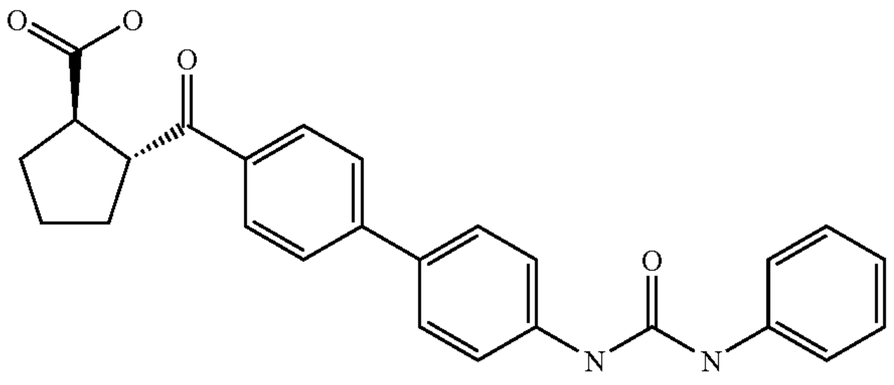

DGAT-1 inhibitor from WO2007137103

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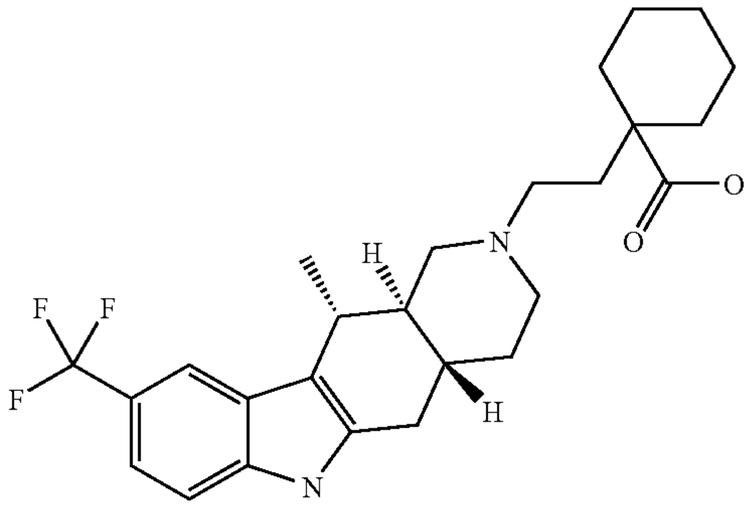

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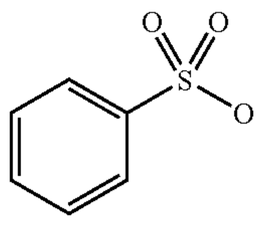

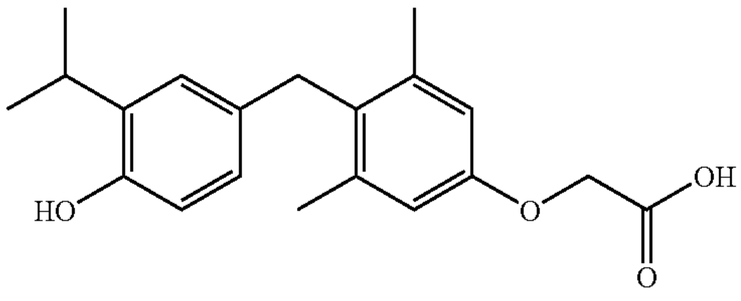

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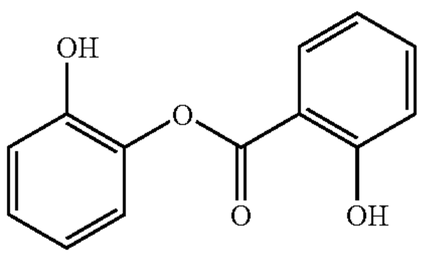

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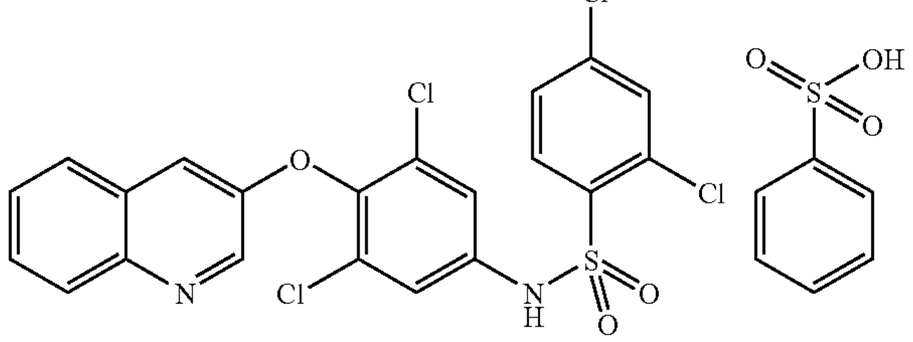
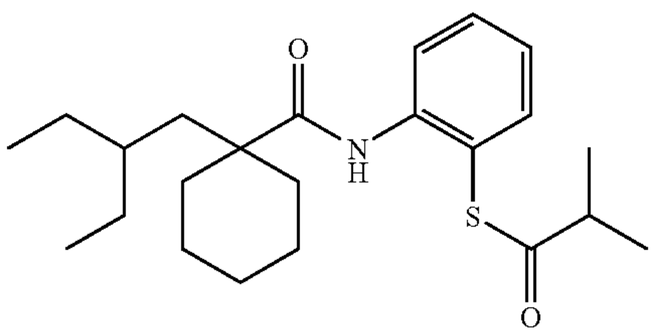


INT-131



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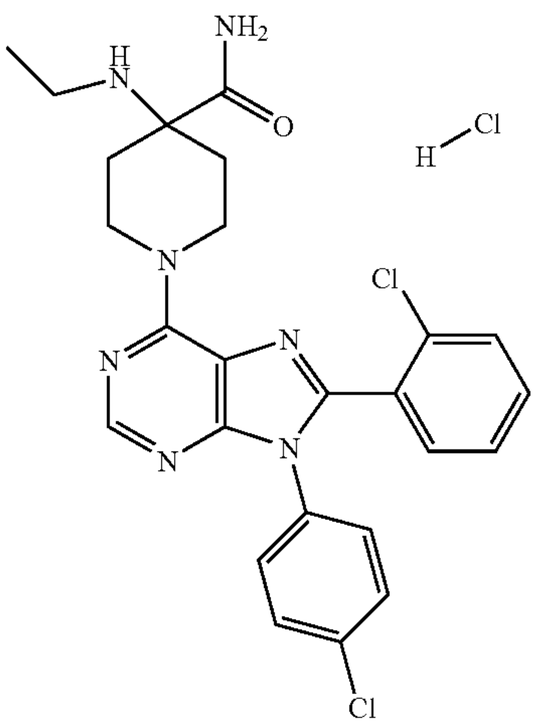

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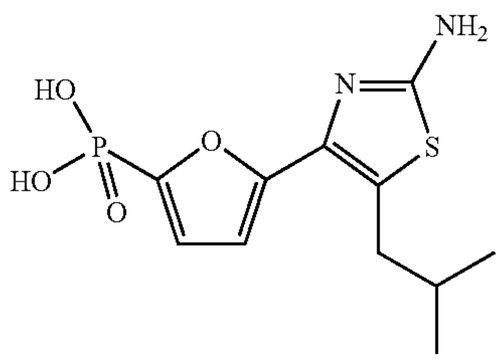

MB-07229

MB-07803

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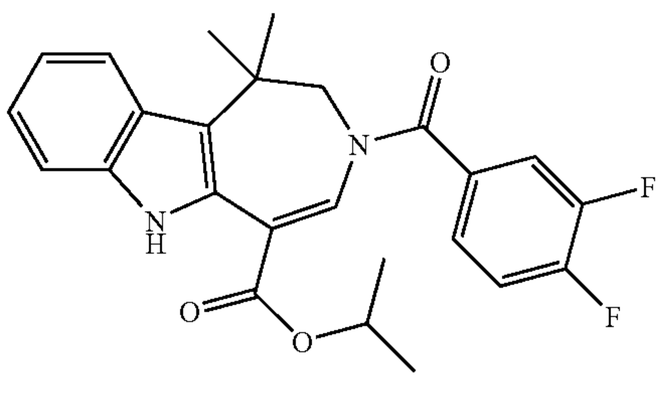
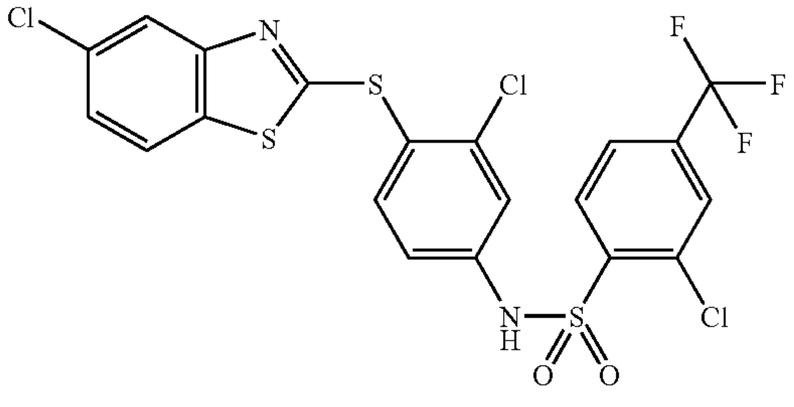


WAY-362450



T-2384

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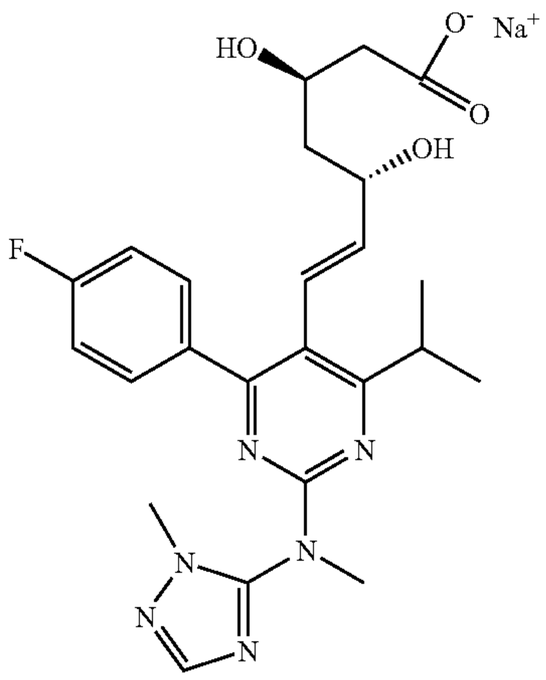


BMS-644950

Also suitable are the following active ingredients for combination preparations:

all antiepileptics specified in the Rote Liste 2007, chapter 15;

all antihypertensives specified in the Rote Liste 2007, chapter 17;

all hypotonics specified in the Rote Liste 2007, chapter 19;

all anticoagulants specified in the Rote Liste 2007, chapter 20;

all arteriosclerosis drugs specified in the Rote Liste 2007, chapter 25;

all beta receptors, calcium channel blockers and inhibitors of the renin angiotensin system specified in the Rote Liste 2007, chapter 27;

all diuretics and perfusion-promoting drugs specified in the Rote Liste 2007, chapter 36 and 37;

all withdrawal drugs/drugs for the treatment of addictive disorders specified in the Rote Liste 2007, chapter 39;

all coronary drugs and gastrointestinal drugs specified in the Rote Liste 2007, chapter 55 and 60;

all migraine drugs, neuropathy preparations and Parkinson's drugs specified in the Rote Liste 2007, chapter 61, 66 and 70.

In one embodiment, the compounds of the formula I are administered in combination with medicaments with effects on the cardiovascular system and the blood vessel system, for example ACE inhibitors (e.g. ramipril), medicaments which act on the angiotensin renin system, calcium antagonists, beta-blockers, etc.

In one embodiment, the compounds of the formula I are administered in combination with antiinflammatory medicaments.

In one embodiment, the compounds of the formula I are administered in combination with medicaments which are used for cancer treatment and cancer prevention.

It will be appreciated that every suitable combination of the compounds of the invention with one or more of the aforementioned compounds and optionally one or more other pharmacologically active substances is regarded as falling within the protection conferred by the present invention.

Test Models

Suitability of the compounds of the invention as active pharmaceutical ingredients can be tested by means of various test models. Descriptions are given of such test models by way of example below.

Influence on the MCH Receptor In Vitro; Determination of Functional IC50 Values of MCH1R Antagonists

Cloning of the cDNA for the human MCH receptor, preparation of a recombinant HEK293 cell line which expresses the human MCH receptor, and functional measurements with the recombinant cell line took place in analogy to the description by Audinot et al. (J. Biol. Chem. 2001, 276, 13554-13562). A difference from the reference was, however, the use of the plasmid pEAK8 from EDGE Biosystems (USA) for the construction of the expression vector. The host used for the transfection was a transformed HEK cell line named "PEAK Stable Cells" (likewise from EDGE Biosystems). Functional measurements of the cellular calcium flux after addition of agonist (MCH) in the presence of ligand of the invention took place with the aid of the FLIPR apparatus from Molecular Devices (USA), using protocols of the apparatus manufacturer. The compounds of the invention show a significant inhibition (>30%) of the signal induced by the agonist at a concentration of 100 μM, preferably at 10 μM, particularly preferably at 1 μM, very particularly preferably at 100 nM and very very particularly preferably at 10 nM.

Besides the functional activity it is also possible to determine the affinity for the MCH1R according to Audinot et al. (Br. J. Pharmacol. 2001, 133, 371-378). Preferred compounds of the invention show an IC50 of less than 1 μM, particularly preferably of less than 100 nM, very particularly preferably of less than 10 nM and very very particularly preferably of less than 1 nM.

Milk Intake by Female NMRI Mice

The anorectic effect is tested on female NMRI mice. After withdrawal of feed for 24 hours, the test substance is administered intraperitoneally or preferably orally by gavage. The animals are housed singly with free access to drinking water and, 30 minutes after administration of product, are offered condensed milk. The condensed milk consumption is determined every half hour for 7 hours, and the general condition of the animals is observed. The measured milk consumption is compared with the vehicle-treated control animals.

The vehicle itself has no influence on feed intake. Preferred tolerated vehicles for the administration are, for example, hydroxyethylcellulose (0.5% in water) or Solutol HS15 (5% in hydroxyethylcellulose (0.5% in water)).

Feed and Water Intake of Female Wistar Rats

As alternative to testing the anorectic effect on NMRI mice, it is also possible analogously to use female Wistar rats weighing about 220-250 g. The animals are accustomed to the experimental environment before the start of the study. In one embodiment, the animals have free access to feed and water up to the start of the experiment. In another embodiment, access of the animals to feed is withdrawn 24 hours before the administration. For the investigation of the test substance, the animals are housed singly with free access to feed and water. Feed intake and water intake are measured continuously

every 30 minutes over a period of 22 hours using a computer-assisted system (TSE Drinking & Feeding Monitor). The measured feed and water consumption is compared with the vehicle-treated control animals.

Body Weight Gain of Diet-Induced Obese and Standard-Fed Mice

For these investigations, male C57BL6J mice 5 weeks old (weaning age) are accustomed either to a standard maintenance diet or to a high-fat and thus high-energy diet. After 12 weeks, the normally fed, slim mice have typically reached a body weight of about 25 g, and the fat-fed mice have reached one of about 35 g. The animals are housed singly, and the feed intake and water intake are determined individually. There is free access to feed and water during the experiment.

The test substances are administered orally in a vehicle and always tested by comparison with the vehicle control which is included in parallel. The vehicle itself has no influence on the feed intake, and is normally hydroxyethylcellulose (0.5% in water) or Solutol HS15 (5% in hydroxyethylcellulose (0.5% in water)). A corresponding group of slim mice is kept for each group of diet-induced obese mice.

Feed consumption and water consumption are determined each day in the first week and then once per week by reweighing the offered feed and water, respectively. The body weight is measured each day.

Blood samples are taken before and at the end of the treatment in order to determine serum parameters which provide information about changes in intermediary metabolism. It is additionally possible to determine the body fat content on the living animal by means of an impedance measurement (TOBEC method).

For the intended effects on parameters such as food uptake and body weight development, it is desirable that an antagonist of MCH1R has sufficient brain penetration (for example determined as the ratio of the compound level in the brain tissue and in the blood serum attained at one time) (on this subject, see, for example, J. Pharmacol. Exp. Thera. 2008, 324, 206-213). Preferred compounds of the invention have a ratio of brain to serum levels of at least 0.3. Further preferred compounds have a ratio of at least 0.6. Particularly preferred compounds exhibit a ratio of at least 1.0.

Micronucleus Test (in vitro)

The aim of the micronucleus test (in vitro) is to examine whether a test compound has the potential to elicit the formation of micronuclei (small membrane-bound DNA fragments) in various cell lines or primary cultures, with or without metabolic activation by S9 liver homogenate. The test system allows differentiation between the clastogenic and aneugenic potential of a test compound by an immunochemical labeling of the kinetochores or by staining the DNA fragments by the FISH (fluorescence in situ hybridization) method.

Brief description: The cells are treated in a 96-well microtiter plate with the test compound. The treatment time is typically 3 hours with metabolic activation or 24 hours without metabolic activation. Twenty-four hours after the end of the treatment, the cells are isolated, fixed and stained. The cytotoxicity of the test compound is assessed according to the relative cell growth expressed as percentage growth or taking account of the doubling time as population doubling compared with the negative control. The highest test concentration should show not less than 30% surviving cells, or should be the concentration at which a precipitate of the test compound is observed. Duplicate determinations should be carried out with each test concentration. An accurate detailed description of the experiment is to be found in Kirsch-Volders et al. (Mutation Res. 2003, 540, 153-163).

Evaluation: The structural or numerical chromosomal damage is reported as the increase in the number of cells with micronuclei in an ensemble of 1000 cells at three analyzable test concentrations. The test is regarded as positive in the following cases:

a) the increase in the number of cells with micronuclei is significant by comparison with the negative control (solvent or untreated), or

b) the number of micronuclei is increased to a biologically relevant extent, concentration-dependently by comparison with the negative control.

A positive control must show a clear statistically significant effect by comparison with the negative control.

Preferred compounds of the invention are negative in the micronucleus test.

AMES II Test

The aim of the AMES II test is to examine whether a test compound has mutagenic potential.

Brief description: A mixed bacterial strain (mixed strains, 6 different *Salmonella typhimurium* strains with in each case a missence point mutation in the histidine operon) and the *Salmonella typhimurium* strain TA98 for detecting frame shift mutations is treated in a 384-well microtiter plate with various concentrations of the test substance with or without metabolic activation through addition of S9 liver homogenate (accurate descriptions of the experiment are to be found in the literature: P. Gee, D. M. Maron, B. N. Ames; Proc. Natl. Acad. Sci. USA 1994, 91, 11606 and Fluckiger-Isler et al.; Mutation Res. 2004, 558, 181 and cit. lit.).

Mutagenic test compounds cause back-mutations and thus restore the functionality of endogenous histidine biosynthesis. Mutated bacteria are thus able to divide and expand to bacterial colonies.

Evaluation: If there is enhanced bacterial growth owing to mutations of the bacteria, then enzymes are digested in the growth medium. As a result, the pH in the medium falls and the color of the added indicator (bromocresol purple) changes from pale violet to yellow. The test is regarded as positive if the number of wells in which a color change is observed per concentration increases significantly by comparison with the control.

Preferred compounds of the invention are negative in the AMES II test.

Cytotoxicity Tests

a) LDH Release

The aim of the test for LDH (lactate dehydrogenase) release is to examine whether a compound damages the integrity of the cell wall and may thus cause cell death.

Brief description: The LDH activity which enters the cell supernatant from the cytosol due to cell damage is measured by colorimetry. The cells are treated with the test compound. Fifty microliters of the culture supernatant are removed and mixed with the reaction solution (LDH kit, Roche, Mannheim) in accordance with the manufacturer's information. LDH catalyzes the conversion of lactate into pyruvate. During this, NAD+ is reduced to NADH/H+. The latter in turn reduces, under the influence of the added diaphorase, a likewise added yellow tetrazolium salt to the red formazan.

Evaluation: The formazan is quantified by measuring the absorption at 492 nM (e.g. with TECAN SPECTRAFluor Plus).

Preferred compounds of the invention show no significant increase in LDH activity at concentrations below 10 μM. Particularly preferred compounds show no increase below a concentration of 50 μM. Even further preferred compounds show no increase below a concentration of 250 μM.

b) Intracellular ATP Content

The aim of the test is to determine the total intracellular ATP content, which is a measure of the energy level and thus the vitality of a cell.

Brief description: 100 μl of cell culture medium are mixed in a well of a microtiter plate with 100 μl of the CellTiter-Glo reagent (following the manufacturer's instructions: Promega Technical Bulletin No. 228, CellTiter-Glo Luminesent Cell Viability Assay). The cultures are shaken at room temperature for 2 minutes and then incubated for 10 minutes until the luminescence signal has stabilized.

Evaluation: The luminescence is recorded, integrating over one second (e.g. with TECAN SPECTRAFluor Plus).

Preferred compounds of the invention show no significant reduction in the ATP levels at concentrations below 10 μM. Particularly preferred compounds show no reduction below a concentration of 50 μM. Even further preferred compounds show no reduction below a concentration of 250 μM.

c) Neutral Red Uptake

The aim of the test is to measure the uptake of neutral red (NR) into the lysosomes/endosomes and vacuoles of living cells, which is a quantitative measure of the number and vitality of the cells.

Brief description: The cells are washed with 150 μl of a preheated phosphate buffer solution (PBS) and incubated with 100 μl of the NR medium at 37° C. in a humidified atmosphere with 7.5% carbon dioxide for 3 hours. After the incubation, the NR medium is removed and the cells are washed with 150 μl of PBS. Removal of the PBS is followed by addition of exactly 150 μl of an ethanol/glacial acetic acid solution. After shaking for 10 minutes, the dye is extracted from the cells to give a homogeneous dye solution. An exact description of the test is to be found in the literature (E. Borenfreund, J. A. Puerner, Toxicol. Lett. 1985, 24(2-3), 119-124).

Evaluation: The absorption of the dye solution is determined at 540 nM using a microtiter plate reader as difference from the absorption of the ethanol/glacial acetic acid solution.

HERG Channel Blockade

The aim of the test is to determine the concentration range in which the test compound blocks the cardiac hERG channel. Blockade of the hERG channel, which is responsible for the Ikr current in the human heart, is associated with potentially fatal arrhythmias.

For expression of the cDNA encoding the hERG channel it was cloned into the pcDNA3 vector (Invitrogen). Chinese hamster oocytes (CHO, American Type Culture Collection, Rockville, Md.) were transfected using lipofectamine (GIBCO/BRL, Grand Island, N.Y.) with the hERG cDNA and selected using G418 (GIBCO/BRL, Grand Island, N.Y.; 500 μg/ml). CHO cells with stable expression of the hERG channel were cultured on a HAM F-12 medium which was supplemented with 10% native bovine serum, 1× penicillin/streptomycin and 500 μg/ml G418 in an atmosphere of 95% air/5% carbon dioxide.

The cells selected for the patch clamp experiment are seeded on a plastic support 18-24 hours before the experiment. HERG channel currents are recorded at room temperature by the whole-cell variant of the patch clamp technique using an Axopatch 200B amplifier (Axon Instruments, Foster City, Calif.). The electrodes (3-6 megaohms resistance) are prepared from TW150F glass capillaries (World Precision Instruments, Sarasota, Fla.) and filled with the pipette solution (120 mM potassium aspartate, 20 mM KCl, 4 mM Na2ATP, 5 mM HEPES, 1 mM MgCl2; adjusted to pH 7.2 with KOH). The hERG channel currents are induced by a positive voltage pulse (20 mV) followed by a negative pulse (−40 mV) and are recorded for later analysis. As soon as the hERG channel current of the cell flushed with the control solution (130 mM, 5 mM KCl, 2.8 mM NaOAc, 1 mM MgCl2, 10 mM HEPES; 10 mM glucose, 1 mM CaCl2; adjusted to pH 7.4 with NaOH) is stable, the cell is perfused with the test compound dissolved in the above control solution (by dilution of a 10 or 100 mM DMSO solution of the test compound so that the DMSO content is no more than 0.1%). The current is followed continuously until no further changes occur. The same procedure is repeated with increasing concentrations of the test compound. The maximum amplitude of the hERG current is measured in picoAmperes (pA) for each concentration and for each cell. The maximum amplitude in pA for each concentration of the test compound is compared with that of the pure control solution in the same cell and calculated as % of the control value.

Evaluation: The test compound is tested at various concentrations in 3-5 CHO cells which express the hERG channel. The IC50 is obtained by use of nonlinear least squares regression (GraphPAD Software, San Diego, Calif.).

General Selectivity

In order to minimize the risk of unwanted side effects, it is desirable to keep the nonselective effect on biologically important functional units (e.g. receptors, ion channels and enzymes; for lists, see, for example, Whitebread, S. et al.; Drug Discovery Today 2005, 10, 1421-33 and Rolland, C. et al.; J. Med. Chem. 2005, 48, 6563-6574) by an active pharmaceutical ingredient as small as possible. General selectivity tests in a large number of in vitro test systems can be carried out by various specialized services (e.g. Cerep, Panlabs).

The compounds of the invention of the formula I exhibit, as selective MCH1R antagonists, selectivity factors of at least 30, preferably of 100, more preferably of 300 and even more preferably of 1000 vis á vis the affinity to other proteins. Examples of such proteins are serotonin receptor subtypes (e.g. the 5-HT2a receptor), muscarine receptor subtypes (e.g. the M1 receptor), adrenergic receptor subtypes (e.g. AR alpha1a), sodium and calcium channels (e.g. the L-type calcium channel).

Solubilities in Aqueous Systems

Adequate solubility of a substance in aqueous solvent systems is an important prerequisite for a (reproducible) pharmacological effect. Solubilities in aqueous systems can be determined by various methods. Suitable examples are solution precipitation methods ("kinetic solubility") and methods which investigate the dissolution of a solid sample until an equilibrium is set up ("thermodynamic solubility").

a) Kinetic Solubility

A DMSO solution of the test compound (2.5 mM; 0.5 μl) is pipetted into 200 μl of an aqueous test solution (e.g. phosphate-buffered saline, 10×, 1M, Sigma, adjusted to 10 mM, pH 7.4) in a 96-well microtiter plate, and the turbidity is measured at the resulting theoretical concentration for the test compound of 6.25 μM using a nephelometer (e.g. Nephelostar Galaxy, BMG Labtech). The concentration of the test compound in the aqueous test solution is then raised to a theoretical 12.5 μM by adding further DMSO solution (2.5 mM; 0.5 μl), and the turbidity measurement is repeated. Further additions of DMSO solutions (1 μl, 2.5 mM; 0.5 μl, 10 mM; then 9×1 μl, 10 mM resulting in theoretical concentrations of 25 μM, 50 μM, 100 μM, 150 μM, 200 μM, 250 μM, 300 μM, 350 μM, 400 μM, 450 μM and 500 μM) with turbidity measurement in between complete the measurement process.

Evaluation: The turbidity values from the nephelometer are plotted against the theoretical concentration of the test compound in the aqueous test solution. As soon as a significant

turbidity is detected (e.g. 5 times above the control value of the aqueous test solution) at a theoretical concentration, the level of concentration below this is stated to be the solubility limit of the test compound in the test solution. Thus, the maximum possible measurement range emerges as values <6.25 μM, 6.25–500 μM and >500 μM.

Preferred compounds of the invention show a kinetic solubility in phosphate buffer (pH 7.4) of at least 12.5 μM; more preferably of at least 50 μM and even more preferably of at least 250 μM.

b) Thermodynamic Solubility

The integrated UV absorption from HPLC UV measurement of serial dilutions of the test compound in DMSO (500 μM, 100 μM, 50 μM, 10 μM and 1 μM) shows a linear correlation with the concentration in a calibration line. The test compound (500 μg) is shaken together with the aqueous test solution (250 μl) in a closed vessel (capacity: 1.5 ml) for 16 hours (Eppendorf thermoshaker, 1400 rpm, 25° C., covering to protect from light). The sample is then centrifuged at maximum rotational speed, and the supernatant is finally filtered. A sample of the filtered supernatant is analyzed directly by HPLC UV measurement (see above). A further sample is analyzed after dilution (1 part by volume of supernatant, 39 parts by volume of test solution).

Evaluation: The concentration of the test compound in the undiluted supernatant is calculated from the resulting integrated UV absorptions of the supernatant samples on the basis of the constructed calibration lines and stated as solubility of the test compound in the respective aqueous test solution.

Examples of aqueous test solutions are deionized water or aqueous phosphate buffer with various pH values (e.g. pH 1.2; pH 4.0; pH 6.8; pH 7.4; pH 9.0) which can be prepared from the commercial solution (phosphate buffered saline, 10×, Sigma) by dilution and adjustment with phosphoric acid or sodium hydroxide solution by standard methods.

Preferred compounds of the invention show a solubility in phosphate buffer (pH 7.4) of at least 12.5 μM; more preferably of at least 50 μM and even more preferably of at least 250 μM.

Permeability

The test for permeability is carried out in CACO-2/TC7 cells which have been cultured (DMEM/Glutamax I/Gibco with high glucose content, HEPES 25 mM, 1% NEAA, 10% FBS, 40 μg/ml gentamycin; 37° C. surrounding temperature; 95% humidity and 10% CO_2 content) on Becton Dickinson filters (24-well, uncoated) for 21 days. The permeability is tested at a concentration of 20 μM for the test compound (1% DMSO in HBSS) with a pH gradient (apical: pH 6.5 and 0.5% BSA; basolateral: pH 7.4 and 5% BSA). Analysis takes place by means of LCMS/MS. Further descriptions of the test system and references for the experimental procedure are to be found in Balimane, P.V.; Drug Discovery Today 2005, 10(5), 335-343.

Inhibition of CYP Enzymes

The inhibition of CYP enzymes is determined on recombinant enzymes (obtained from Becton Dickinson) and fluorescent substrates (BD/Gentest) as recommended by the manufacturer (see Website http://www.bdbiosciences.com). Further descriptions of the test system and references for the experimental procedure are to be found in Zlokarnik, G.; Drug Discovery Today 2005, 10(21), 1443-1450.

Metabolic Stability

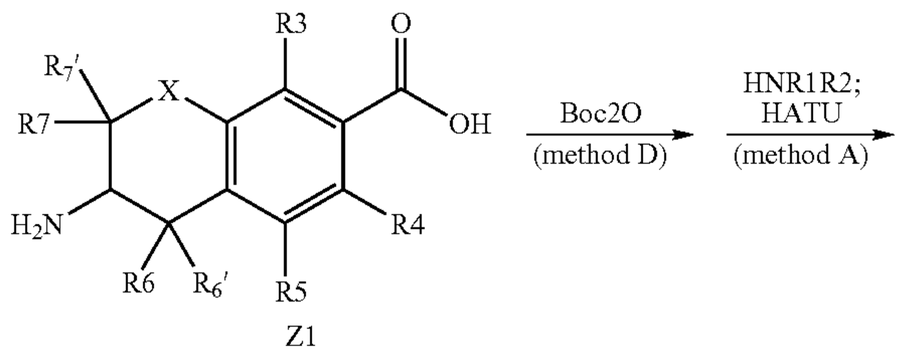
The metabolic stability is determined by incubating the test compound (5 μM) with microsomal liver fractions (1 mg/ml protein with 0.1% w/v BSA; 1 mM NADPH, 0.5% DMSO) at 37° C. Analysis at an incubation time of 0 and 20 minutes takes place by means of LCMS/MS. Further descriptions of the test system and references for the experimental procedure are to be found in Plant, N.; Drug Discovery Today 2004, 9(7), 328-336 and Lau, Y. Y. et al.; Pharmaceutical Res. 2002, 19(11), 1606-1610.

EXAMPLES

The examples and preparation methods adduced below serve to illustrate the invention, but without limiting it.

The inventive compounds of the formula I can be prepared with the aid of reactions known in principle. For example, an amino acid of the structure Z1 can first be protected selectively (for example by method D with Boc2O). The subsequent reaction with an amine (HNR1R2) can advantageously be carried out using a commonly known coupling reagent (for example by method A-1 with HATU or by method A-2 with EDC/HOBt). Removal of the protecting group (for example by method C with hydrochloric acid) and subsequent reduction (for example by method B with lithium aluminum hydride) gives rise to an amine of structure Z2 (where R8=H). When one carbamate protecting group is not removed before the reduction, Z2 is obtained with R8=methyl. In a last step, the inventive compounds of the formula Ia can be obtained by reducing the amine Z2 with an acid of the structure B-L3-A-L2-CO2H (for example by method A-1 or A-2) (scheme 1).

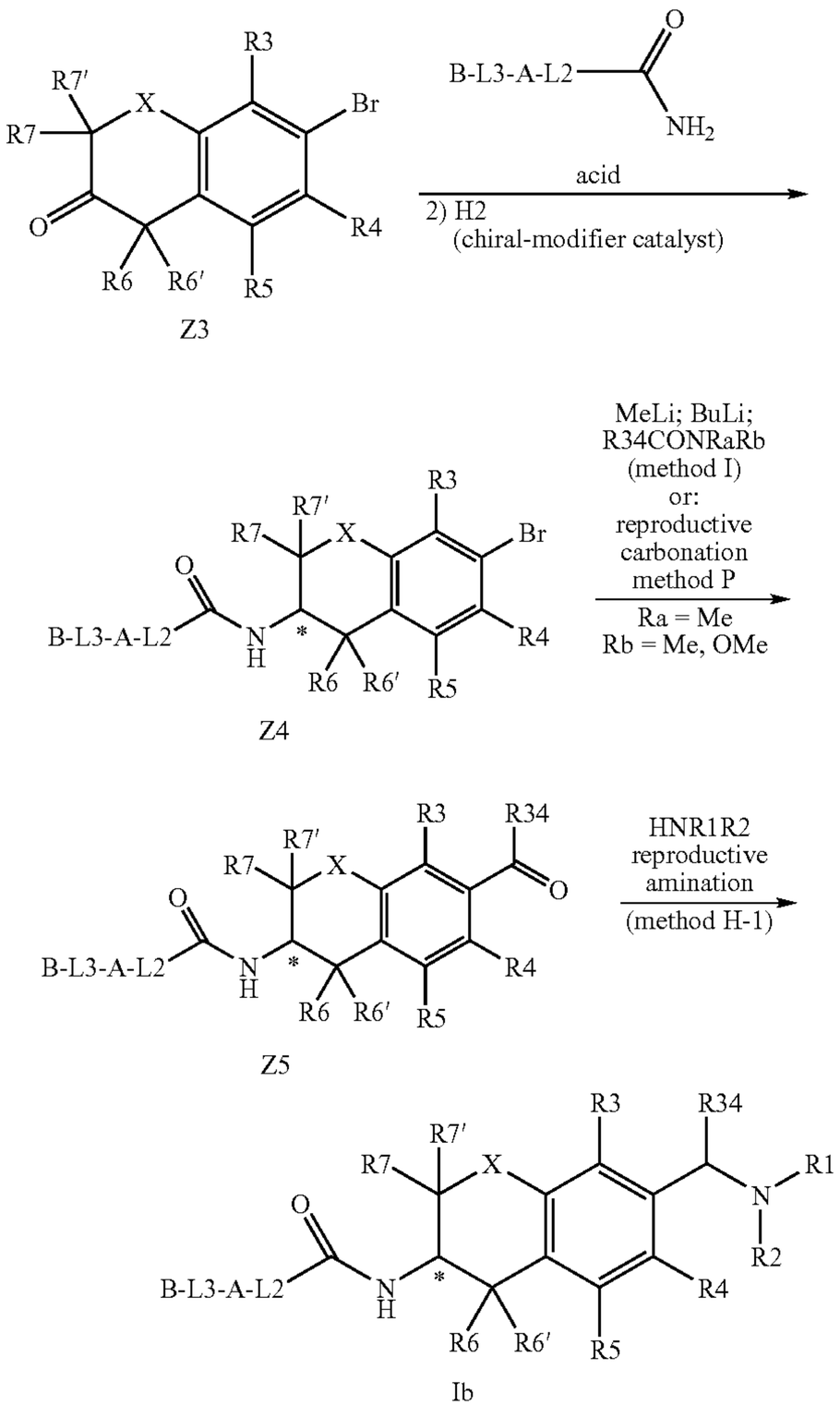
Scheme 1



Further compounds of the type Ia can be obtained by reacting the intermediates Z2 with carboxylic acids of the structure HO-A-L2-COOH (for example by method A-2) and subsequent alkylation with appropriate alkylating agents (for example by method F with alkyl bromides, alkyl iodides or alkylsulfonic esters).

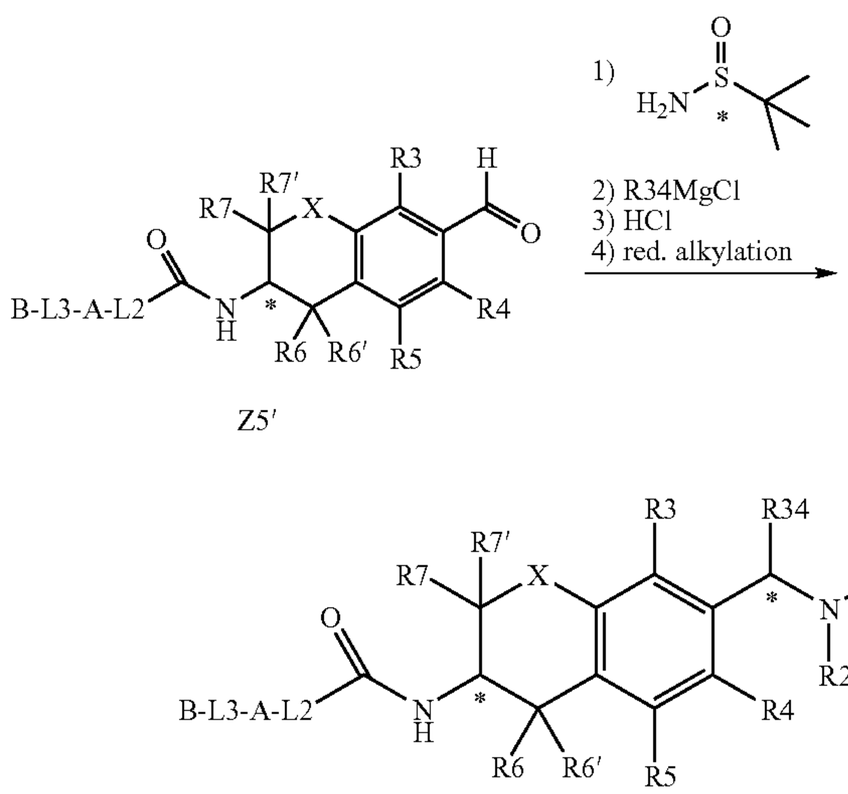
Alternatively, compounds of the formula I can be obtained from the ketones Z3, which are commercially available, or can be prepared by known methods (see, for example, synthesis 2004, 121; J. Org. Chem. 1995, 60, 4324). Acid-catalyzed condensation of the ketones Z3 with amides (B-L3-A-L2-CONH2) and subsequent (optionally asymmetric) catalytic hydrogenation of the resulting enamides under known conditions (see, for example, Adv. Synth. Catal. 2003, 345, 230; Tetrahedron: Asymmetry 1999, 10, 3467; J. Org. Chem. 1995, 60, 4324) gives rise to the aryl bromides Z4. These can be converted by literature methods to the arylcarbonyl compounds Z5 (see, for example, J. Am. Chem. Soc. 2000, 122, 6935; J. Med. Chem. 2005, 48, 1948; Angew. Chem. Int. Ed. 2006, 45, 154). Final reductive amination leads to the compounds Ib (scheme 2).

Scheme 2



Stereochemically defined compounds of type Ib* can be formed, for example, by condensation of the intermediates Z5' with chiral sulfinylamides (for example by method M), addition of Grignard reagents (for example by method L), hydrolysis (for example by method K) and optional reductive alkylation, for example by method H-2 (scheme 2-1).

Scheme 2-1



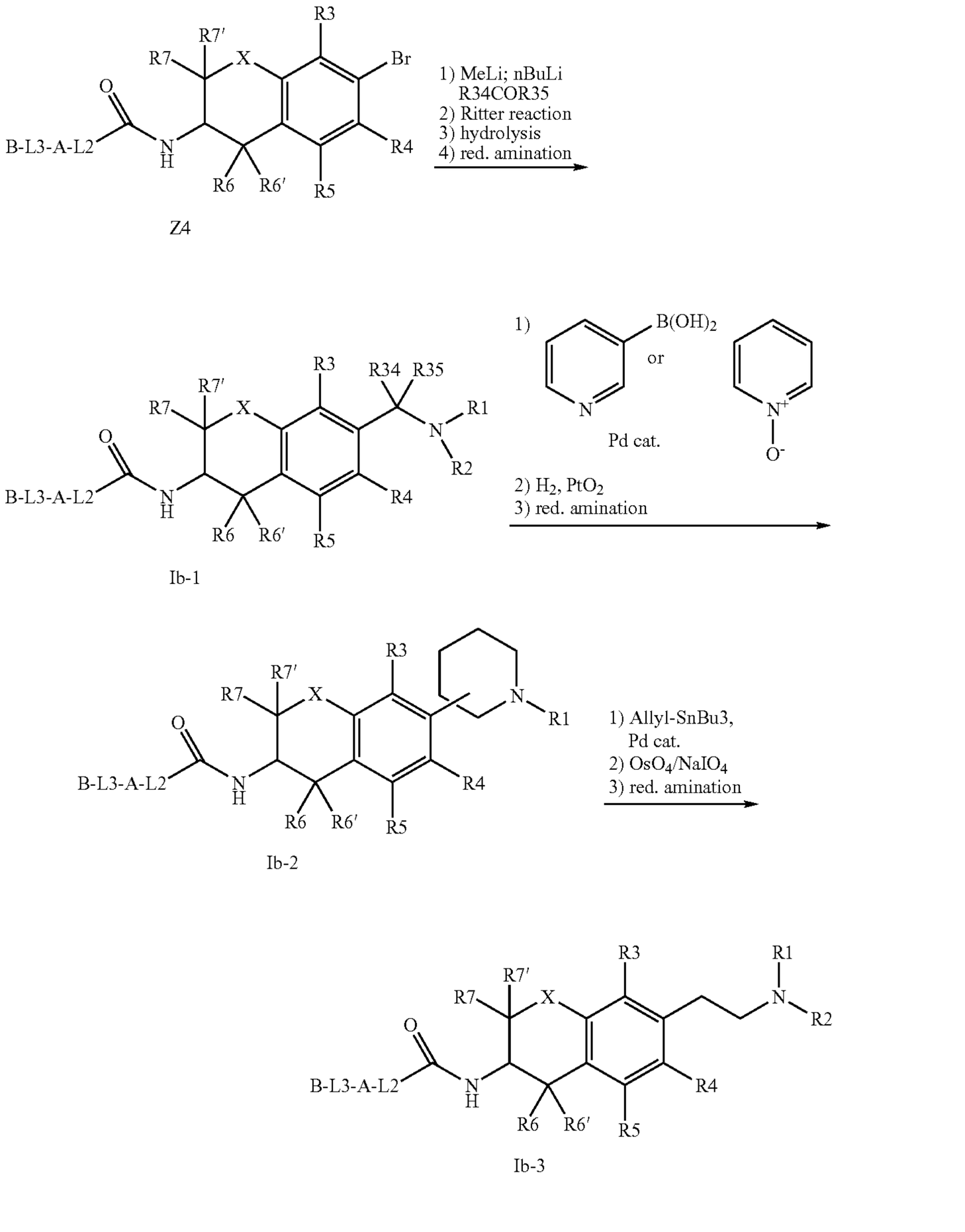
Further intermediates of the Z4 type can be obtained by subsequent modification of substituents. For example, methoxy groups (B-L3=MeO) can be cleaved by reagents such as hydrogen bromide or boron tribromide (for example by method N), and the resulting aromatic hydroxyl compounds can be reacted with appropriate alkylating agents (for example by method F with alkyl bromides, alkyl iodides or alkyl sulfonates).

The intermediates Z4 can also be used to synthesize other compounds of the formula I. For this purpose, for example, the dian ions obtained by sequential treatment of Z4 with MeLi and then n-BuLi can be reacted with ketones (R34COR35). The resulting tertiary alcohols can be converted under the conditions of the Ritter reaction (e.g. TMSCN, H2SO4/HOAc to amides which then, after hydrolysis and optional reductive amination, give rise to compounds of the structure Ib-1 (scheme 2-2).

Alternatively, the intermediates Z4 can also be reacted by means of transition metal complexes (for example those of Pd and Ni) catalyzed with pyridyl compounds (e.g. pyridyltrialkyltin compounds, pyridylboronic acid (derivatives) or pyridine N-oxides). Subsequent hydrogenation with suitable catalysts (e.g. PtO2 in HOAc; method J-1) and optional reductive alkylation gives rise to the structures Ib-2 (scheme 2-2).

In another variant, the intermediates Z4 are reacted with allyl-metal compounds (e.g. allyltributyltin) under palladium catalysis, then the double bond is cleaved oxidatively (for example with $OsO4/NaIO_4$), and the aldehydes thus obtained are reacted with amines HNR1R2 in the sense of a reductive amination (scheme 2-2).

Scheme 2-2



Z4

Ib-1

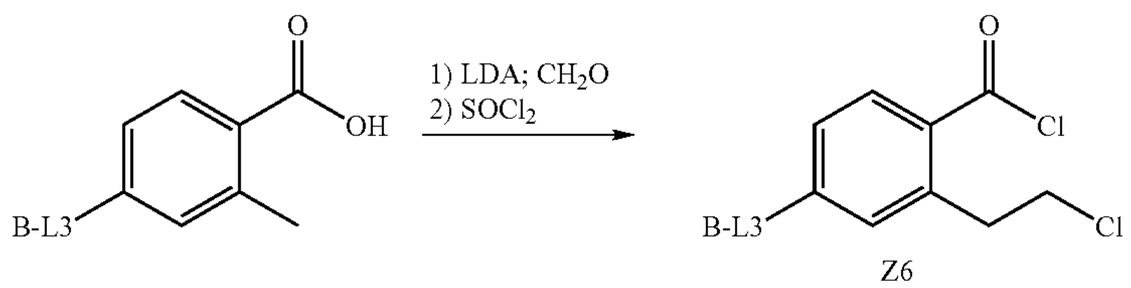
Ib-2

Ib-3

Alkylation (for example with NaH, MeI) on the amide function of the intermediates Z4, Z5 and Z5' and further synthesis along the pathways specified above, and also analogous alkylation of the structures Ib, Ib-1, Ib-2 and Ib-3, give rise to further routes to compounds of the formula I (variation of the substituent R8).

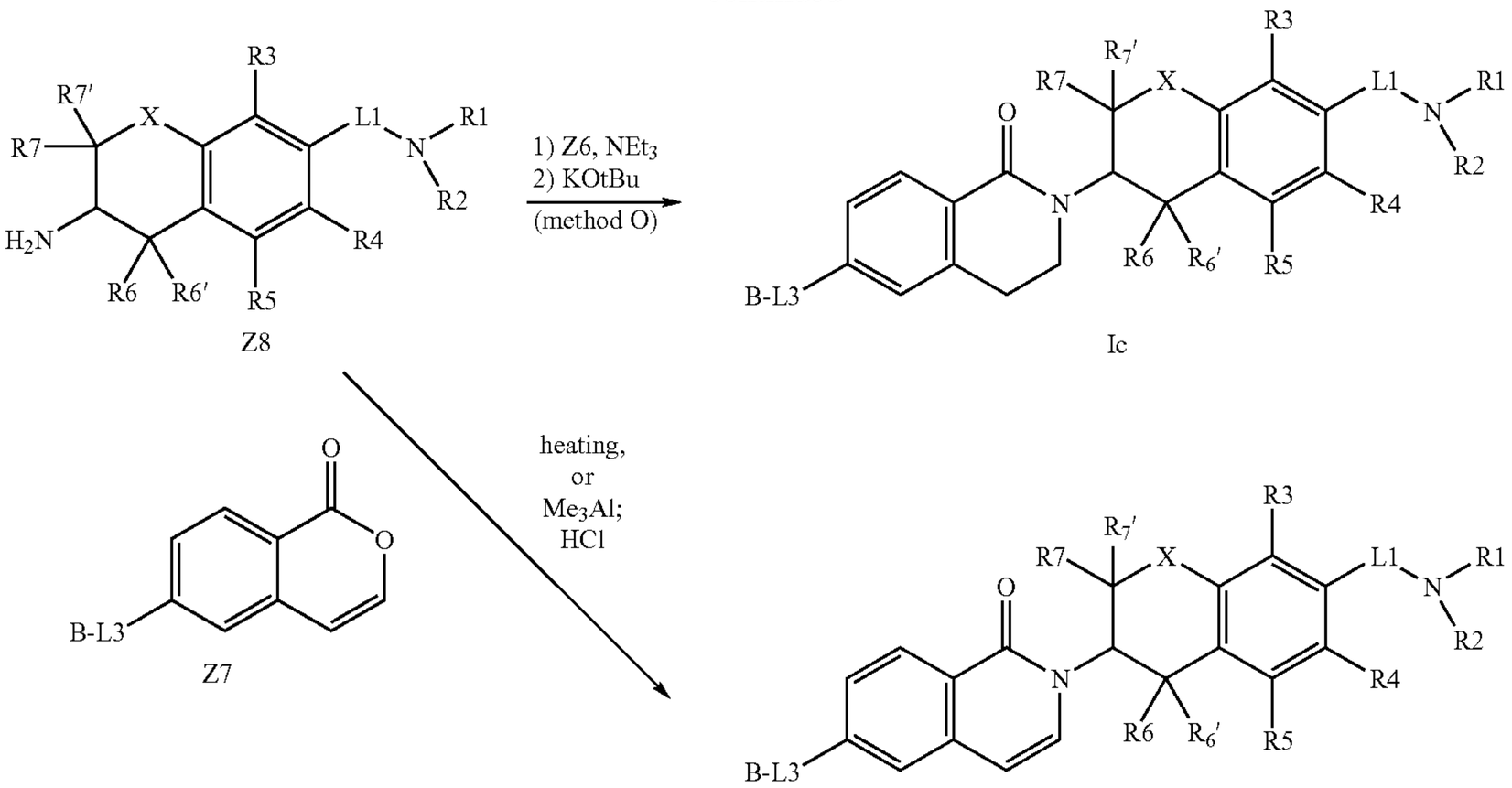
A further preparation process for other compounds of the formula I again consists in reacting dichlorides of the Z6 type or isochromenones of the Z7 type with amines Z8 by processes known in principle (scheme 3). The dichlorides Z6 required can be obtained from ortho-methylbenzoic acids by double metalation, for example with lithium diisopropylamide (LDA), scavenging of the dianion with formaldehyde (for example in the form of paraformaldehyde) and final dichlorination. The amines Z8 can be obtained, for example, according to scheme 1 (Z2 with R8=H) or according to scheme 2 by hydrolysis of the structures Ib.

Scheme 3



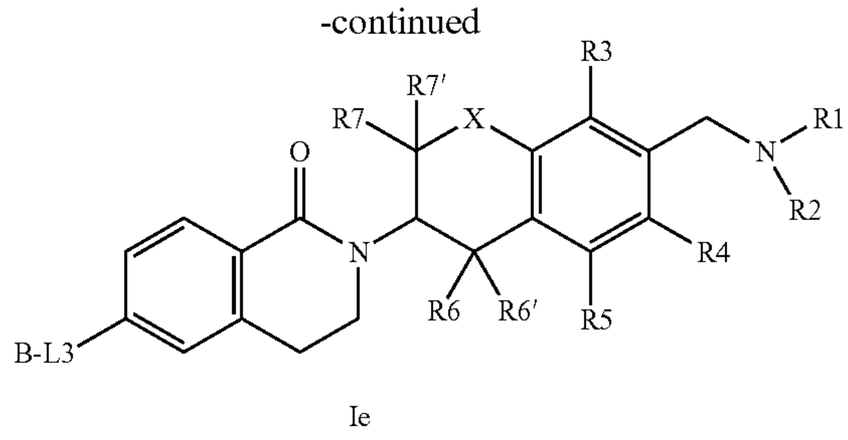
Z6

-continued



Alternatively, for the synthesis of (dihydro)isoquinolinones of the formula I, it is also to possible to cleave the amide bond of the intermediates Z4 under appropriate conditions (for example with HBr/methanesulfonic acid). The amines thus obtained can be reacted with the dichlorides Z6 (or the isochromenones Z7). The bromides Z9 thus prepared can then be converted further to inventive compounds analogously to the intermediates Z4 (preferably by means of the transition metal-catalyzed reactions specified there). For example, the bromides Z9 can be reductively carbonylated and the aldehydes thus obtained can be converted to compounds of the Ie type by means of a reductive amination (scheme 3-1).

-continued



Descriptions of the general methods used can be found, by way of example, at the following points:
method A-1, B, C, D, E, F, G in example 1;
method H, I in example 2;
method J-1 in example 4;
method K, L, M-1 in example 6;
method H-2 in example 8-1;
method A-2 in example 9-1;
method N in example 13;
method O in example 14;
method P in example 15.

General Explanations

a) Drawing of the Structural Formulae

In the structural formulae of the examples given, for clarity, preferentially only non-hydrogen atoms are shown.

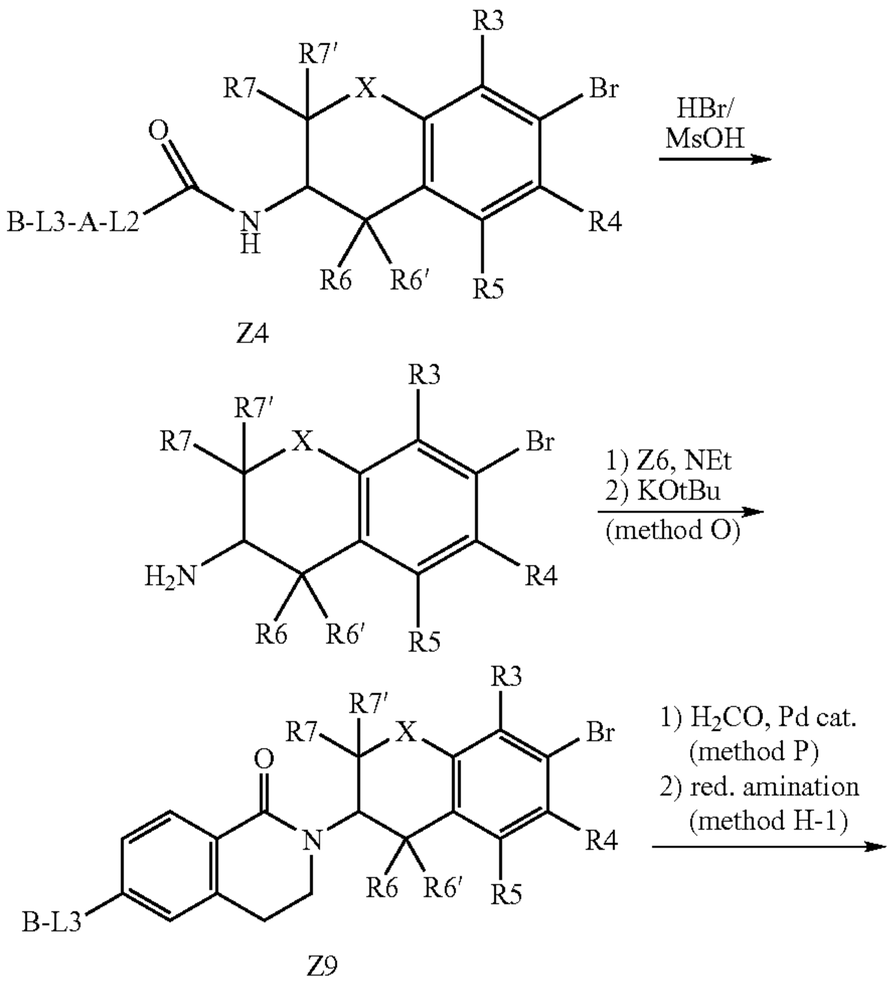
b) Salt Forms

Many of the inventive compounds are bases and can form salts with correspondingly strong acid. In particular, the compounds, after HPLC purification using an eluent comprising trifluoroacetic acid, may be present in the form of hydrotrifluoroacetates. These can be converted to the free bases shown by simple treatment of a solution of the salts, for example with sodium carbonate solution.

c) Units of the Characterization Data

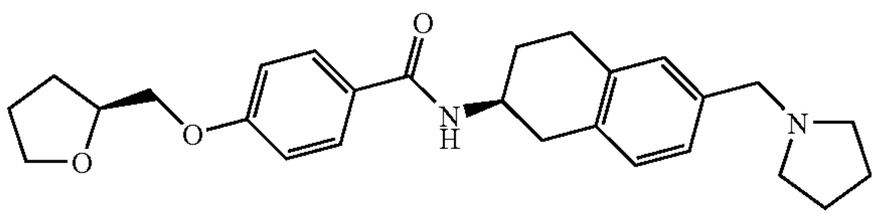
The unit of the molecular weights reported is "g/mol". Peaks observed in the mass spectrum are reported as the integer quotient of the molar molecular ion mass and the charge of the molecular ion (m/z).

Scheme 3-1



Example 1

N-((S)-6-Pyrrolidin-1-ylmethyl-1,2,3,4-tetrahydronaphthalen-2-yl)-4-[(S)-1-(tetrahydrofuran-2-yl) methoxy]benzamide



Method A-1

To a solution of 4-[(S)-1-(TETRAHYDROFURAN-2-YL) METHOXY]BENZOIC ACID (3.38 g) in NMP (30 ml) were added HATU (O-(7-AZABENZOTRIAZOL-1-YL)-N,N,N',N'-TETRAMETHYLURONIUM HEXAFLUOROPHOSPHATE; 5.78 g) and then triethylamine (2.12 ml). A solution of (S)-6-pyrrolidin-1-ylmethyl-1,2,3,4-tetrahydronaphthalen-2-ylamine (3.5 g) in NMP (20 ml) was added dropwise. After 12 hours, the reaction mixture was diluted with ethyl acetate, washed with saturated sodium carbonate solution and concentrated. The residue was purified by chromatography on silica gel (eluent: 10:1 DCM/MeOH). The product was thus obtained with the molecular weight of 434.58 (C27H34N2O3); MS (ESI): 435 (M+H+).

(S)-6-Pyrrolidin-1-ylmethyl-1,2,3,4-tetrahydronaphthalen-2-ylamine

Method B

A solution of ((S)-6-amino-5,6,7,8-tetrahydronaphthalen-2-yl)pyrrolidin-1-yl-methanone (0.49 g) in THF (5 ml) was added dropwise to a suspension of lithium aluminum hydride (0.60 g) in THF (10 ml). The mixture was stirred at RT for one hour. Water (0.6 ml) was cautiously added dropwise, followed by sodium hydroxide solution (16%; 2 ml) and water again (2 ml). The resulting precipitate was filtered off and the filtrate was concentrated. The residue was taken up in hydrochloric acid (1N) and the solution was washed with diethyl ether. The aqueous phase was basified with concentrated sodium hydroxide solution and extracted three times with dichloromethane (DCM). The combined organic phases were dried over magnesium sulfate and concentrated. The product was thus obtained with the molecular weight of 230.36 (C15H22N2); MS (ESI): 231 (M+H+). In an analogous manner, (S)-6-(4-methoxypiperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-2-ylamine and (S)-6-azepan-1-ylmethyl-1,2,3,4-tetrahydronaphthalen-2-ylamine were prepared.

((S)-6-Amino-5,6,7,8-tetrahydronaphthalen-2-yl)-pyrrolidine-1-ylmethanone

Method C

To a solution of [(S)-6-(pyrrolidine-1-carbonyl)-1,2,3,4-tetrahydronaphthalen-2-yl]-carbamic acid tert-butyl ester (0.70 g) in MeOH (5 ml) was added concentrated hydrochloric acid (5 ml). After one hour, the mixture was basified with concentrated sodium hydroxide solution and extracted three times with DCM. The combined organic phases were dried over magnesium sulfate and concentrated. The product was thus obtained with the molecular weight of 244.34 (C15H20N2O); MS (ESI): 245 (M+H+).

[(S)-6-(Pyrrolidine-1-carbonyl)-1,2,3,4-tetrahydronaphthalenr-2-yl]carbamic Acid tert-butyl Ester

According to method A-1, (S)-6-tert-butoxycarbonylamino-5,6,7,8-tetrahydronaphthalene-2-carboxylic acid was reacted with pyrrolidine. The product was thus obtained with the molecular weight of 344.46 (C20H28N2O3); MS (ESI): 345 (M+H+).

(S)-6-tert-Butoxycarbonylamino-5,6,7,8-tetrahydronaphthalene-2-carboxylic Acid

Method D

To a mixture of (S)-6-amino-5,6,7,8-tetrahydronaphthalene-2-carboxylic acid (1.0 g), sodium hydroxide solution (32%; 1.1 g) and MeOH (20 ml) was added DI-TERT-BUTYL DICARBONATE (1.92 g). The mixture was stirred at 50° C. for 6 hours and then water (150 ml) was added. After extraction with diethyl ether, the aqueous phase was acidified slightly and extracted three times with DCM. The combined organic phases were dried over magnesium sulphate and concentrated. The product was thus obtained with the molecular weight of 291.35 (C16H21NO4); MS (ESI): 292 (M+H+).

4-[(S)-1-(Tetrahydrofuran-2-yl)methoxy]benzoic Acid

Method E

A mixture of 4-[(S)-1-(tetrahydrofuran-2-yl)methoxy] benzoic acid methyl ester (9.8 g), sodium hydroxide solution (2 N; 80 ml) and MeOH (300 ml) was stirred for 12 hours. Organic volatile fractions were removed on a rotary evaporator. The remaining aqueous phase was extracted with methyl tert-butyl ether (MTBE) and then acidified with concentrated hydrochloric acid. The resulting precipitate was filtered off and dried. The product was thus obtained with the molecular weight of 222.24 (C12H14O4); MS (ESI): 223 (M+H+).

4-[(S)-1-(Tetrahydrofuran-2-yl)methoxy]benzoic Acid Methyl Ester

Method F

A mixture of methanesulfonic acid (S)-1-(tetrahydrofuran-2-yl)methyl ester (7.6 g), 4-hydroxybenzoic acid methyl ester (6.4 g), cesium carbonate (20 g) and NMP (100 ml) was heated to 75° C. for 12 hours. The cooled reaction mixture was admixed with water and extracted with ethyl acetate. The organic phase was washed three times with water, dried over magnesium sulfate and concentrated. The product was thus obtained with the molecular weight of 236.27 (C13H16O4); MS (ESI): 237 (M+H+).

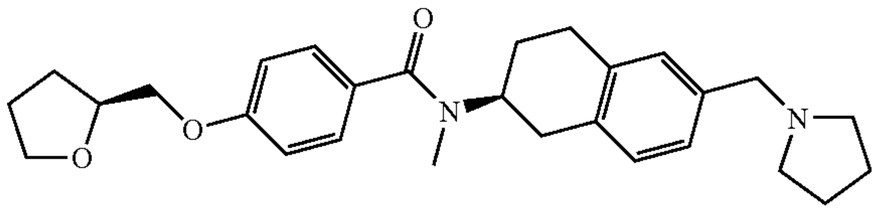
Methanesulfonic acid (S)-1-(tetrahydrofuran-2-yl)methyl Ester

Method G

To a solution of (S)-1-(tetrahydrofuran-2-yl)methanol (7.95 g) in pyridine (35 ml) was added, at −15° C., methanesulfonyl chloride (7.47 g), and the reaction was stirred at 0° C. for 5 hours. After the addition of water, the mixture was extracted with ethyl acetate. The organic phases were dried over magnesium sulfate and concentrated. The product was thus obtained with the molecular weight of 180.22 (C6H12O4S); MS (ESI): 181 (M+H+). Analogously, methanesulfonic acid (R)-1-(tetrahydrofuran-2-yl)methyl ester was synthesized.

Example 2

N-Methyl-N-((S)-6-pyrrolidin-1-ylmethyl-1,2,3,4-tetrahydronaphthalen-2-yl)-4-[(S)-1-(tetrahydrofuran-2-yl)methoxy]benzamide



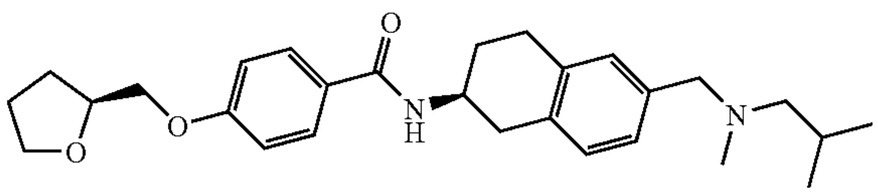
According to method A-1,4-[(S)-1-(TETRAHYDROFURAN-2-YL)METHOXY]-BENZOIC ACID was reacted with methyl-((S)-6-pyrrolidin-1-ylmethyl-1,2,3,4-tetrahydronaphthalen-2-yl)amine. The product was thus obtained with the molecular weight of 448.61 ($C_{28}H_{36}N_2O_3$); MS (ESI): 449 ($M+H^+$).

Methyl-((S)-6 pyrrolidin-1-ylmethyl-1,2,3,4-tetrahydronaphthalen-2-yl)amine

According to method B, [(S)-6-(pyrrolidine-1-carbonyl)-1,2,3,4-tetrahydro-naphthalen-2-yl]carbamic acid tert-butyl ester was reacted with lithium aluminum hydride (10 equiv., 60° C., 2 hours). The product was thus obtained with the molecular weight of 244.38 ($C_{16}H_{24}N_2$); MS (ESI): 245 ($M+H^+$).

Example 3-1

N-{(S)-6-[(Isobutylmethylamino)methyl]-1,2,3,4-tetrahydronaphthalen-2-yl}-4-[(S)-1-(tetrahydrofuran-2-yl)methoxy]benzamide



Method H-1

To a mixture of N-((S)-6-formyl-1,2,3,4-tetrahydronaphthalen-2-yl)-4-[(S)-1-(tetrahydrofuran-2-yl)methoxy]benzamide (0.50 g), THF (5 ml), methanol (2 ml), isobutylmethylamine (0.23 g) and acetic acid (0.24 g) was added polymer-bound sodium cyanoborohydride (2.7 mmol), and the suspension was agitated at room temperature for 12 hours. The polymer was filtered off with suction and the filtrate was concentrated. The residue was purified by preparative HPLC. The product was thus obtained with the molecular weight of 450.63 ($C_{28}H_{38}N_2O_3$); MS (ESI): 451 ($M+H^+$).

N-((S)-6-Formyl-1,2,3,4-tetrahydronaphthalen-2-yl)-4-[(S)-1-(tetrahydrofuran-2-yl)methoxy]benzamide

Method I

A mixture of N-((S)-6-bromo-1,2,3,4-tetrahydronaphthalen-2-yl)-4-[(S)-1-(tetrahydrofuran-2-yl)methoxy]benzamide (10.0 g) and THF (130 ml) was cooled to −78° C. (dry ice bath) and a solution of methyl lithium (18.9 ml; 1.6 M in diethyl ether) was added dropwise. One minute after the addition had ended, a solution of butyllithium (13.9 ml; 2.5 M in toluene) was added dropwise. One minute after the addition had ended, DMF (5.1 g) was added, and, after a further 30 seconds, acetic acid (4.5 ml). After warming to room temperature, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic phases were dried over magnesium sulfate and concentrated. The product was thus obtained with the molecular weight of 379.46 ($C_{23}H_{25}NO_4$); MS (ESI): 380 ($M+H^+$). In an analogous manner, N-((R)-6-formyl-1,2,3,4-tetrahydronaphthalen-2-yl)-4-[(S)-1-(tetrahydrofuran-2-yl)methoxy]benzamide was prepared from N-((R)-6-bromo-1,2,3,4-tetrahydronaphthalen-2-yl)-4-[(S)-1-(tetrahydrofuran-2-yl)methoxy]benzamide.

N-((S)-6-Bromo-1,2,3,4-tetrahydronaphthalen-2-yl)-4-[(S)-1-(tetrahydrofuran-2-yl)methoxy]benzamide

According to method F, N-((S)-6-bromo-1,2,3,4-tetrahydronaphthalen-2-yl)-4-hydroxybenzamide was reacted with methanesulfonic acid (S)-1-(tetrahydrofuran-2-yl)methyl ester. The product was thus obtained with the molecular weight of 430.35 ($C_{22}H_{24}BrNO_3$); MS (ESI): 430 ($M+H^+$).

N-((S)-6-Bromo-1,2,3,4-tetrahydronaphthalen-2-yl)-4-hydroxybenzamide

A mixture of N-((S)-6-bromo-1,2,3,4-tetrahydronaphthalen-2-yl)-4-methoxybenzamide (3.0 g), glacial acetic acid (2 ml) and HBr (20 ml; 48% in water) was heated to 150° C. in a closed glass vessel in a microwave reactor for 25 minutes. The precipitate obtained after the cooling was filtered off. The product was thus obtained with the molecular weight of 346.23 ($C_{17}H_{16}BrNO_2$); MS (ESI): 346 ($M+H^+$). Both N-((S)-6-bromo-1,2,3,4-tetrahydronaphthalen-2-yl)-4-methoxybenzamide and N-((R)-6-bromo-1,2,3,4-tetrahydronaphthalen-2-yl)-4-methoxybenzamide were obtained by literature methods (J. Org. Chem. 1995, 60, 4324).

The examples compiled in table 1 were obtained by reacting the appropriate carbonyl compounds (aldehydes or ketones) with the appropriate amines by method H-1.

TABLE 1

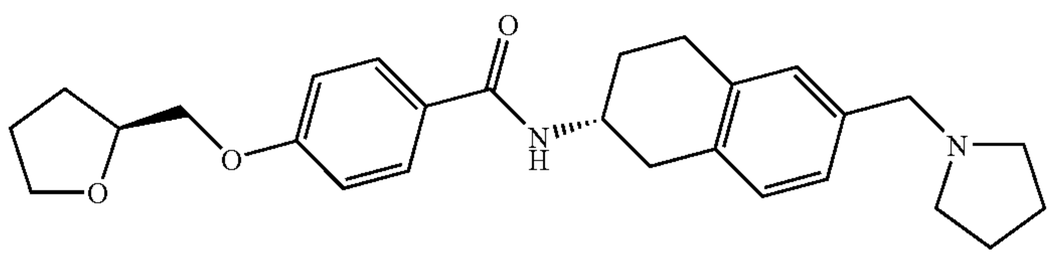
Ex. No.	Structure	Molecular-weight	ESI-MS $[M+H]^+$
3-2		434.58	435

TABLE 1-continued

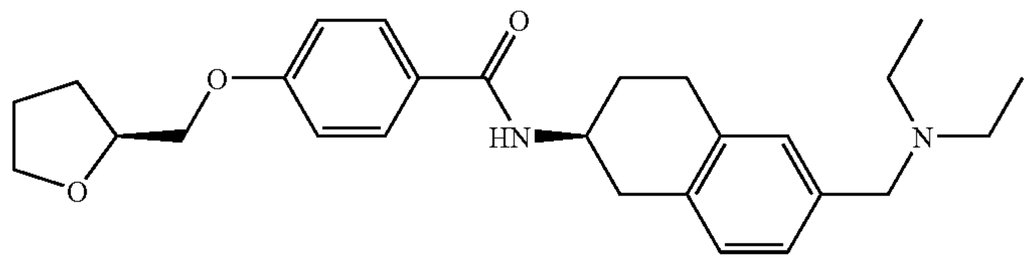
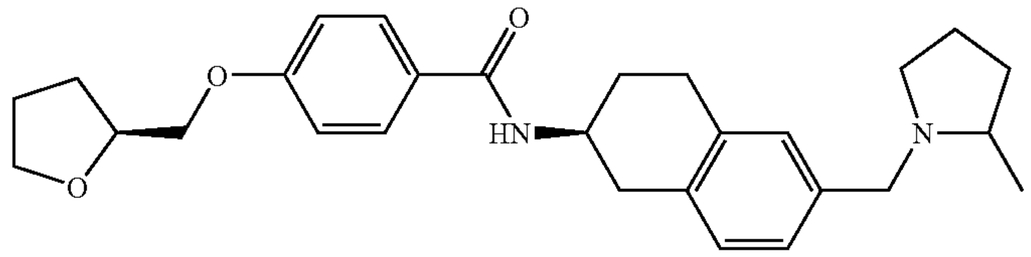
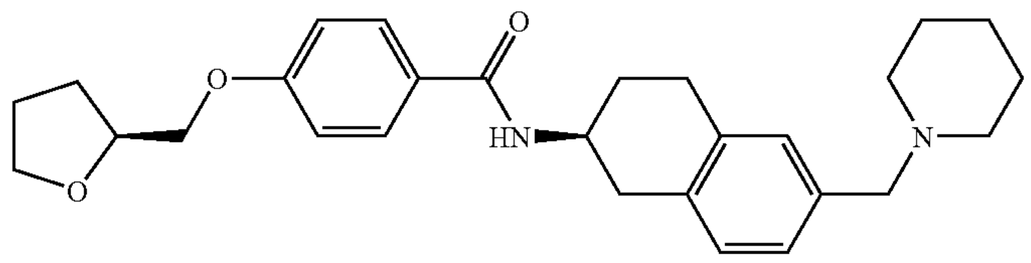
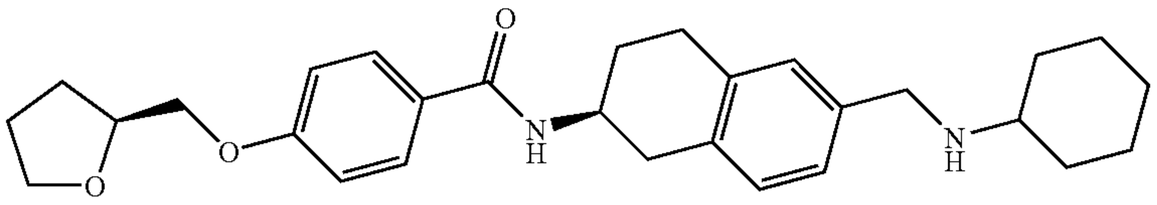
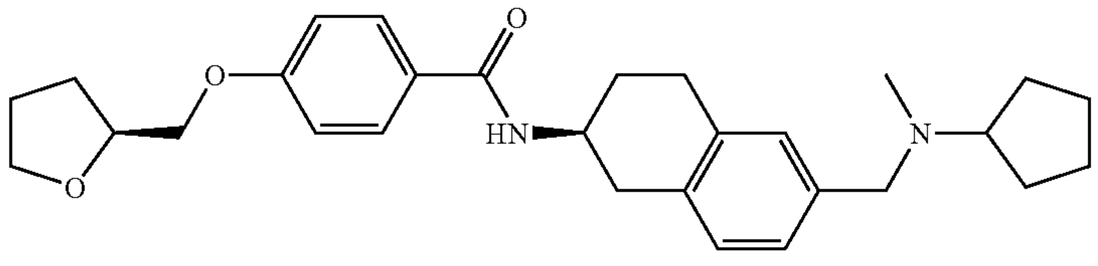
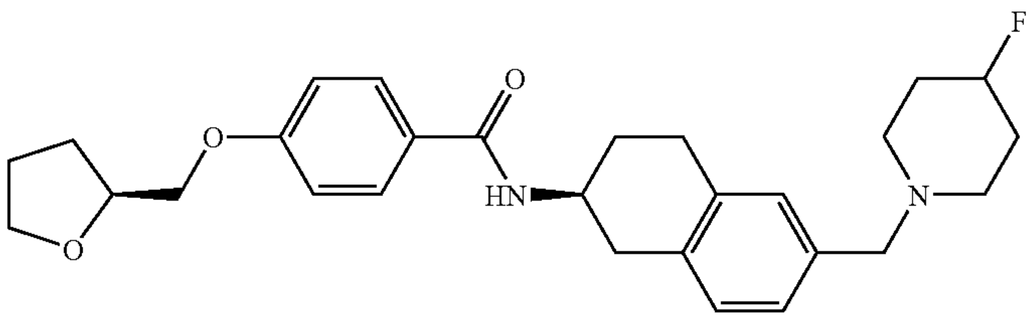
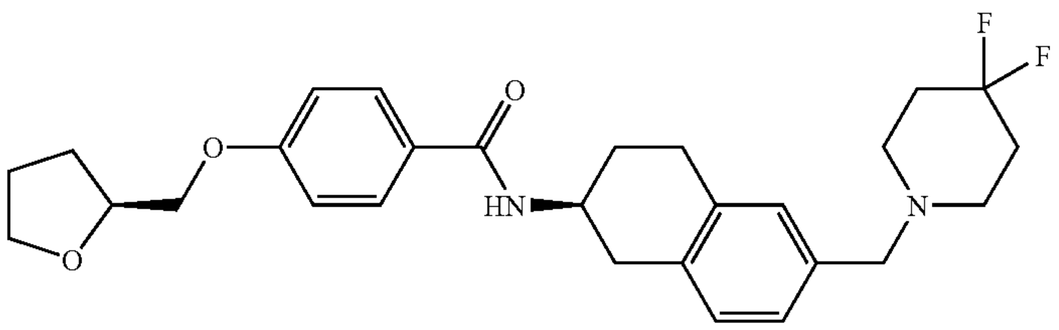
Ex. No.	Structure	Molecular-weight	ESI-MS $[M + H]^+$
3-3		436.59	437
3-4		448.60	449
3-5		448.60	449
3-6		462.63	463
3-7		462.63	463
3-8		462.63	463
3-9		466.59	467
3-10		484.58	485

TABLE 1-continued

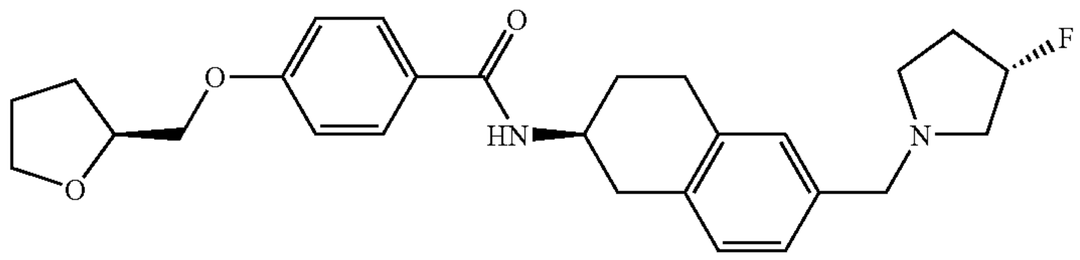
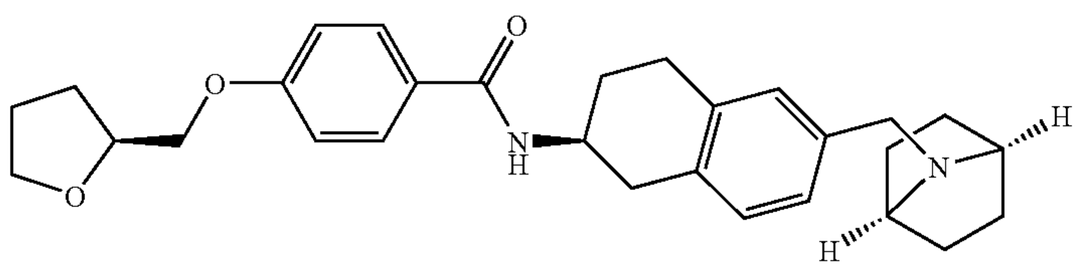
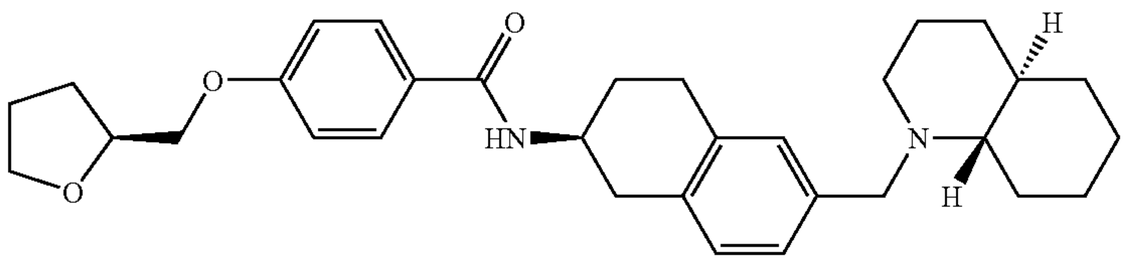
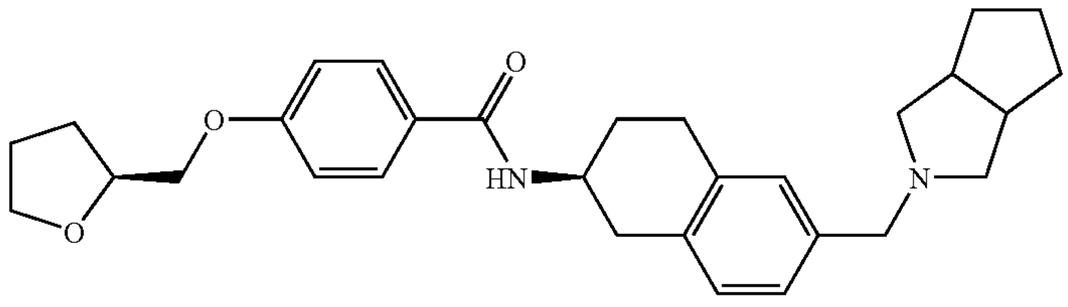
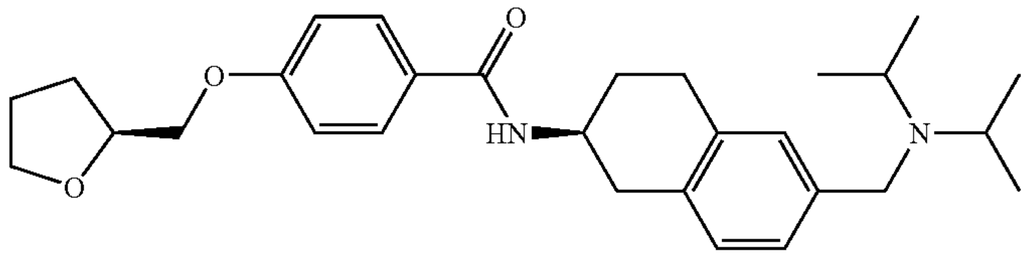
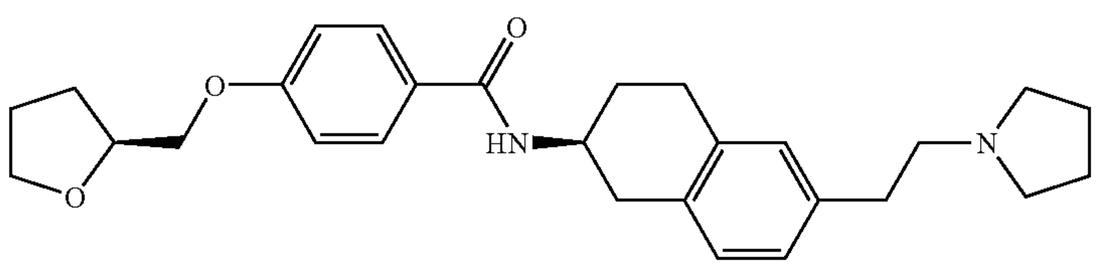
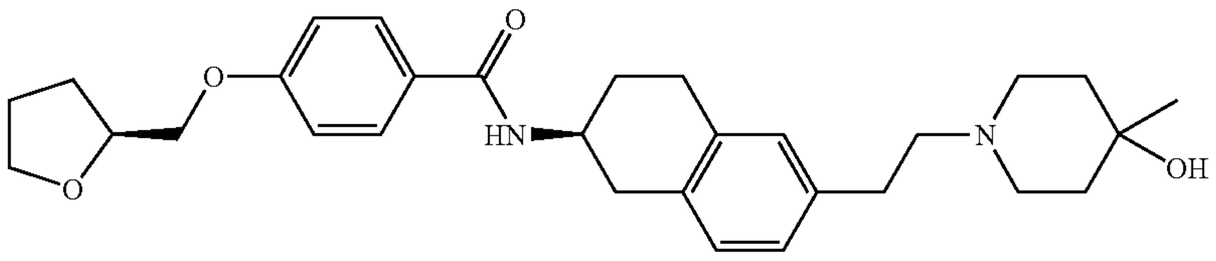
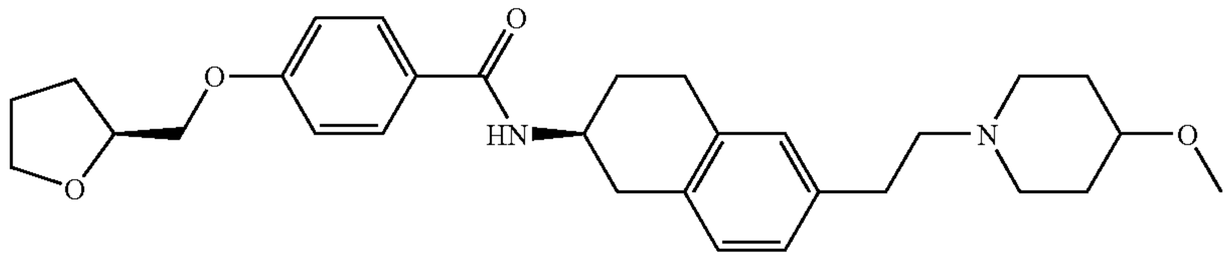
Ex. No.	Structure	Molecular-weight	ESI-MS $[M + H]^+$
3-11		452.57	453
3-12		460.61	461
3-13		502.70	503
3-14		474.64	475
3-15		464.65	465
3-16		448.60	449
3-17		492.66	493
3-18		492.66	493

TABLE 1-continued

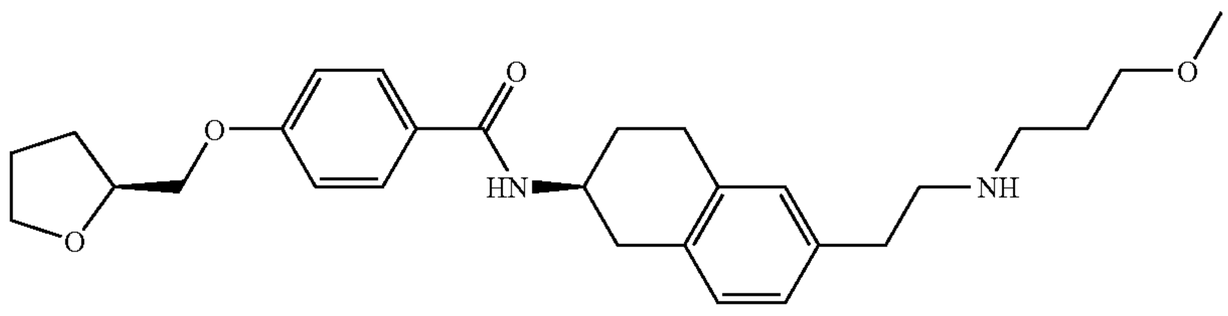
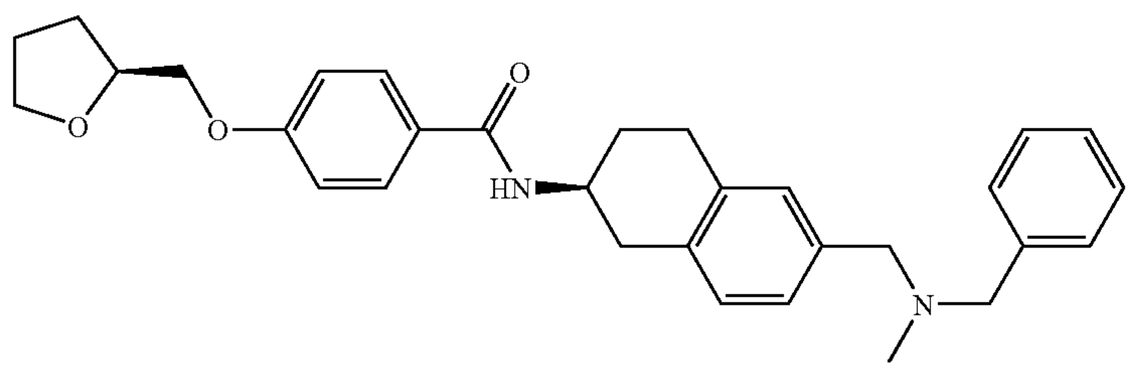
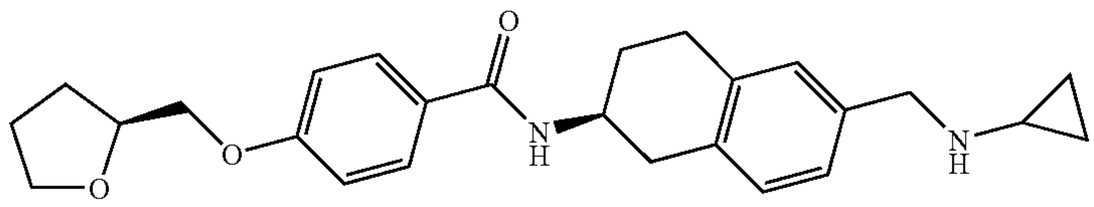
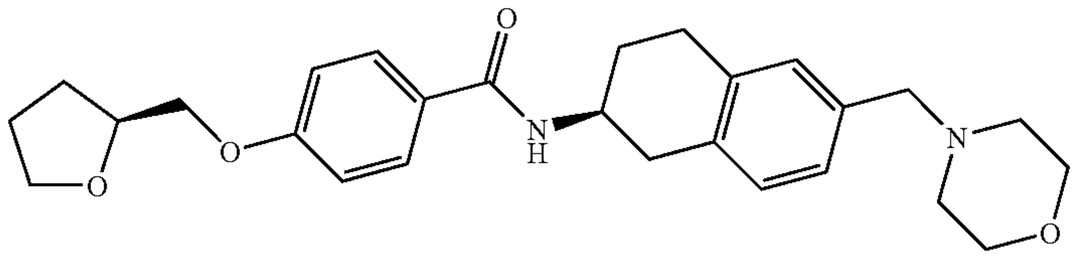
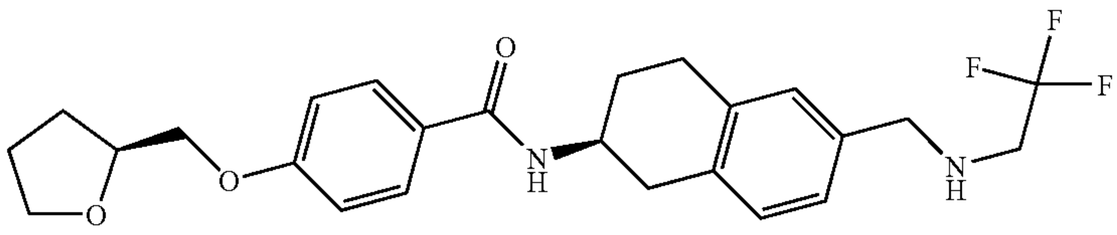
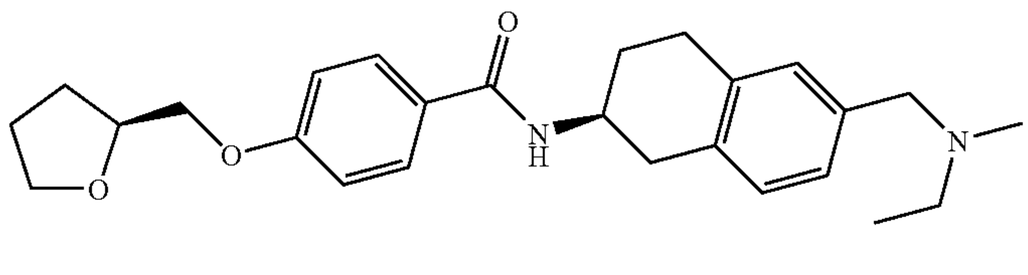
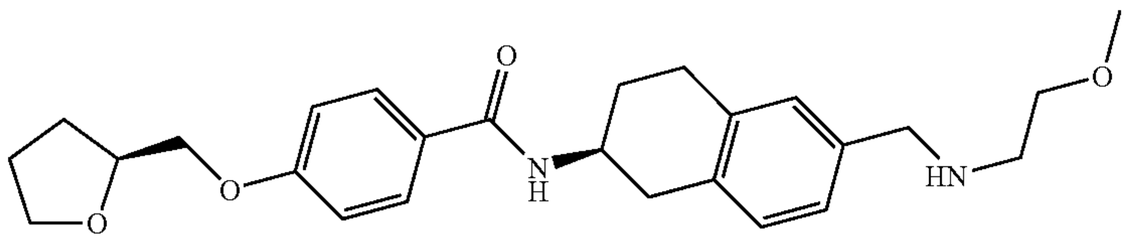
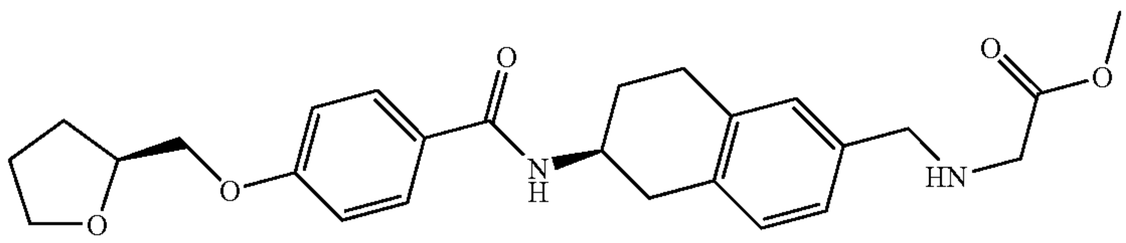
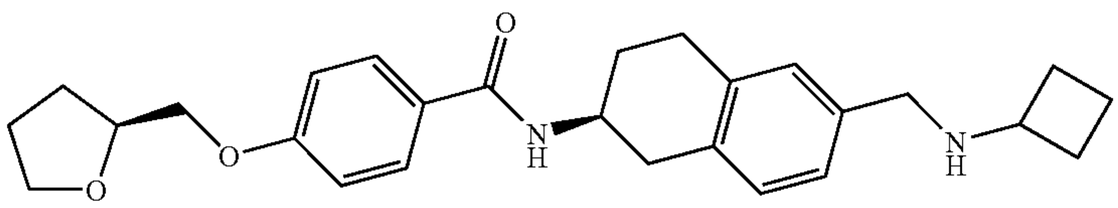
Ex. No.	Structure	Molecular-weight	ESI-MS $[M + H]^+$
3-19		466.62	467
3-20		484.64	485
3-21		420.55	421
3-22		450.58	451
3-23		462.51	463
3-24		422.57	423
3-25		438.57	439
3-26		452.55	453
3-27		434.58	435

TABLE 1-continued

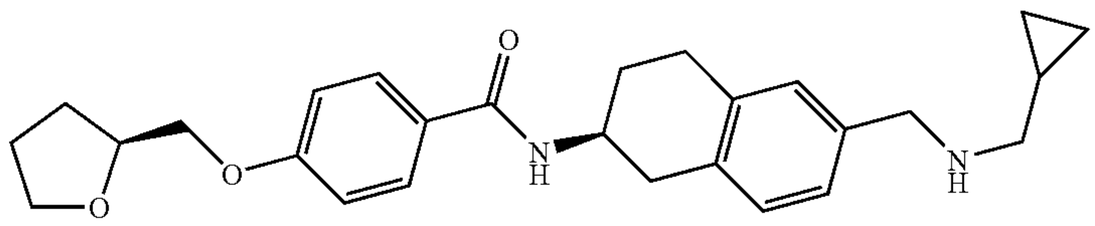
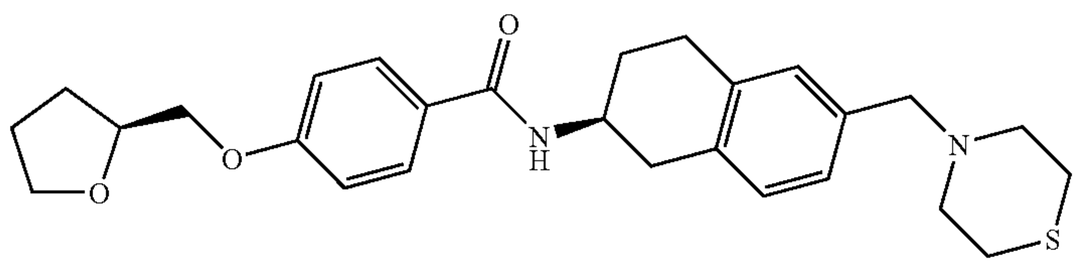
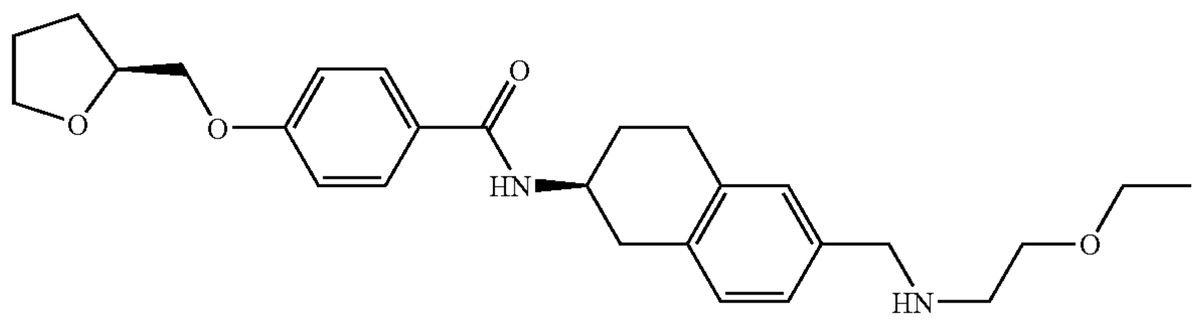
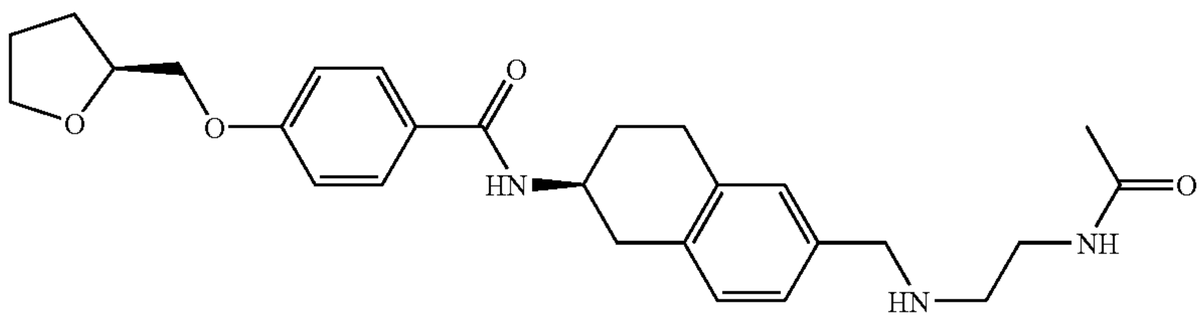
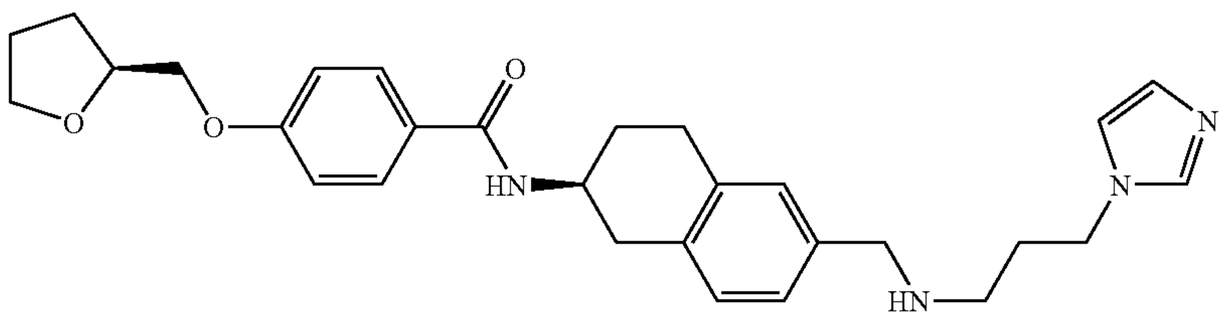
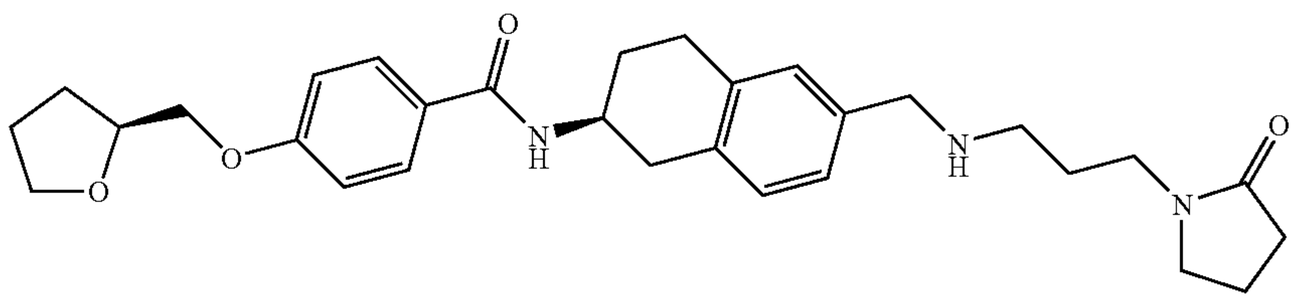
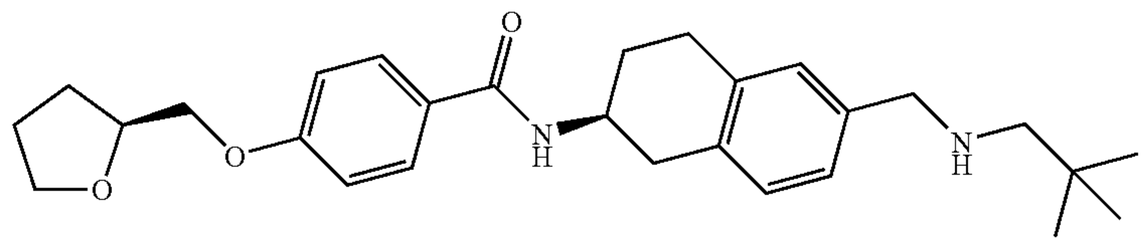
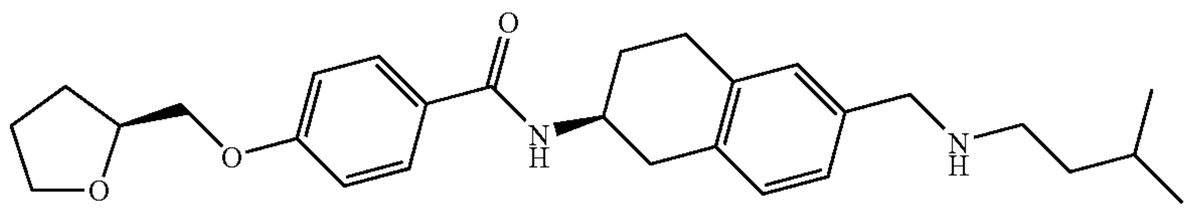
Ex. No.	Structure	Molecular-weight	ESI-MS $[M + H]^+$
3-28		434.58	435
3-29		466.64	467
3-30		452.59	453
3-31		465.59	466
3-32		488.63	489
3-33		505.66	506
3-34		450.62	451
3-35		450.62	451

TABLE 1-continued

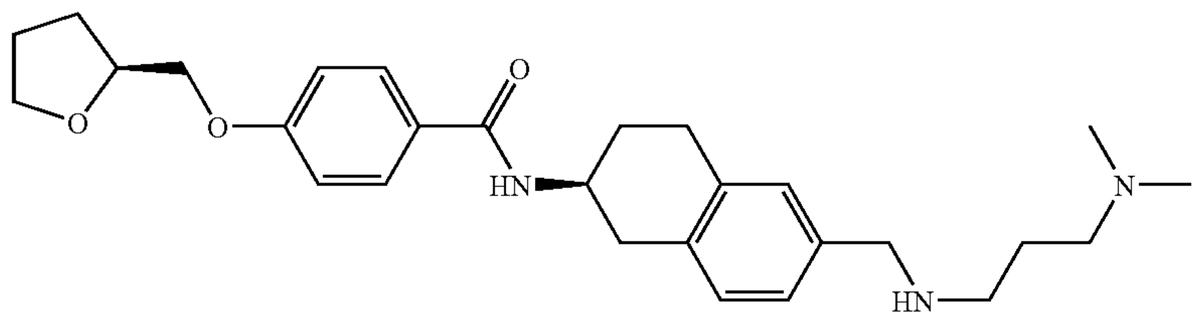
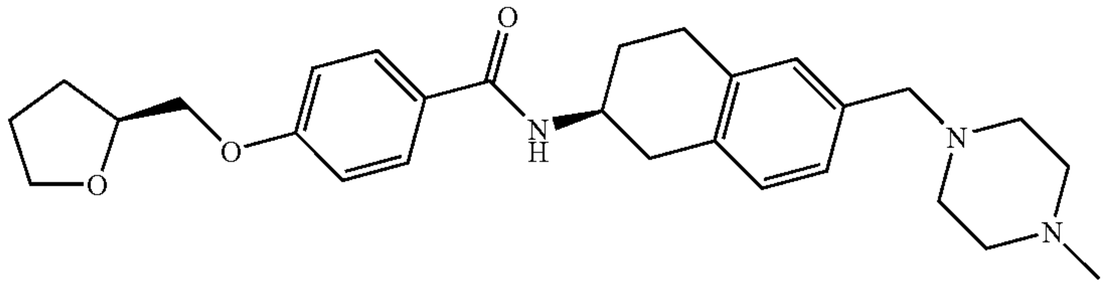
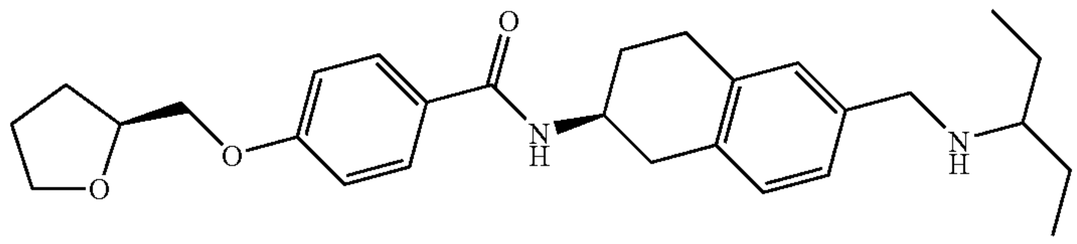
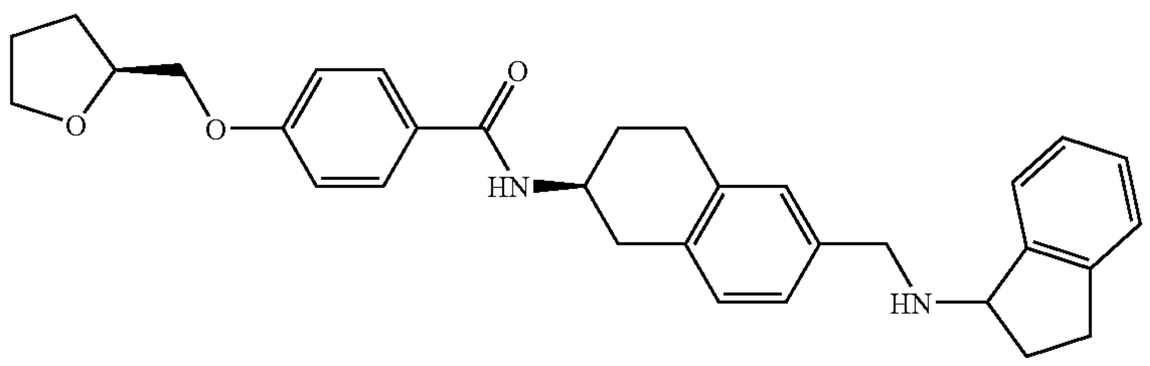
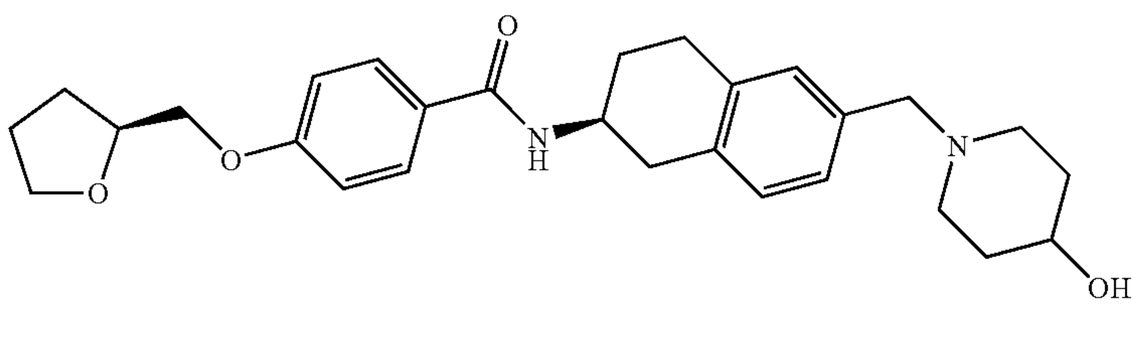
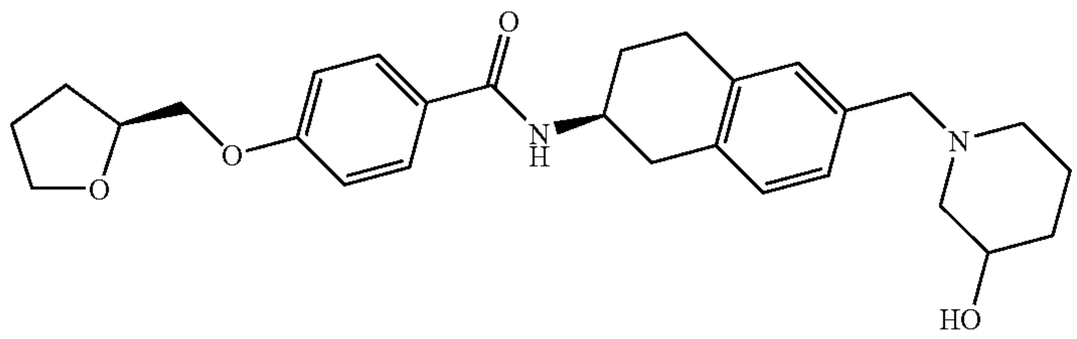
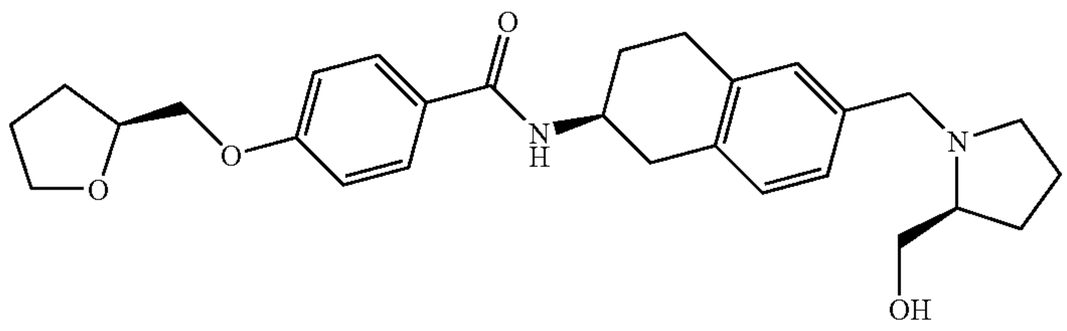
Ex. No.	Structure	Molecular-weight	ESI-MS $[M + H]^+$
3-36		465.63	466
3-37		463.62	464
3-38		450.62	451
3-39		496.65	497
3-40		464.60	465
3-41		464.60	465
3-42		464.60	465

TABLE 1-continued

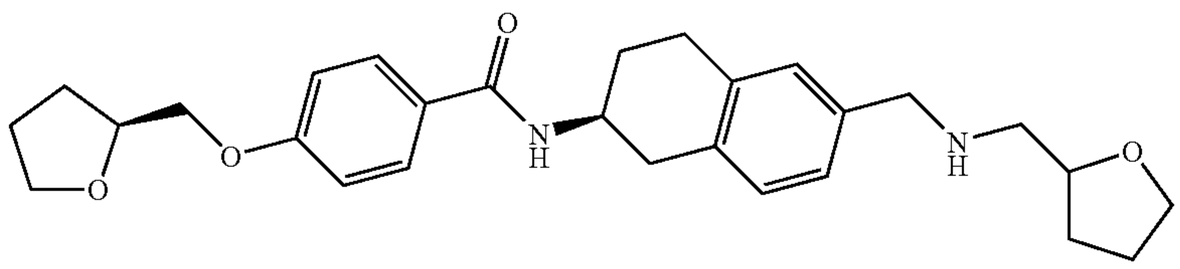
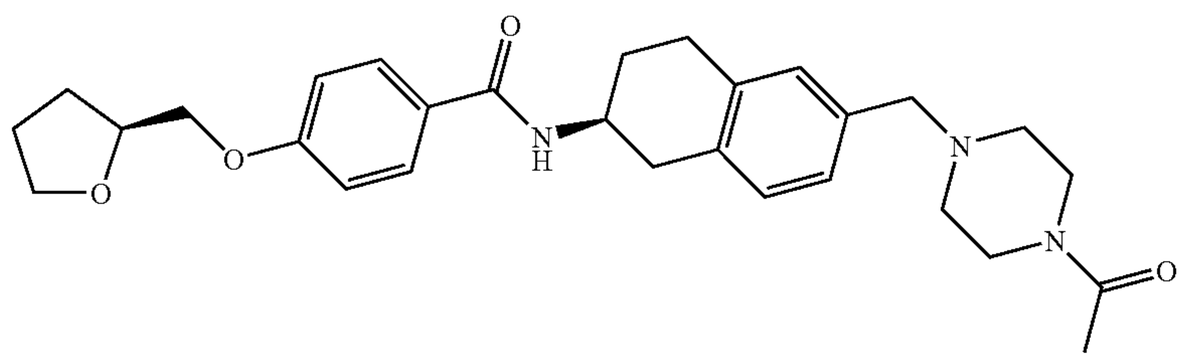
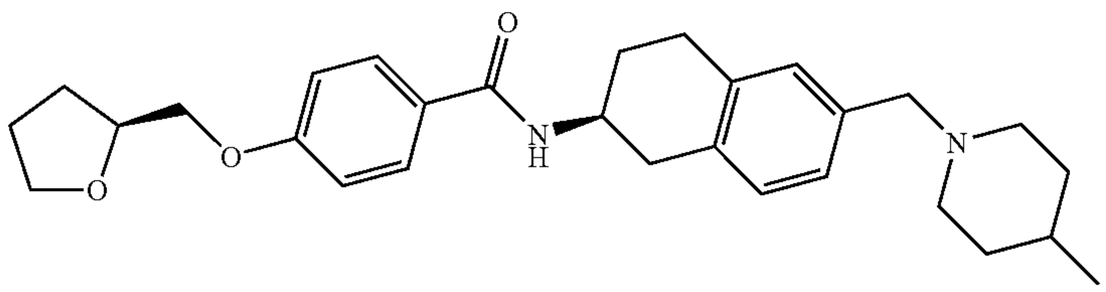
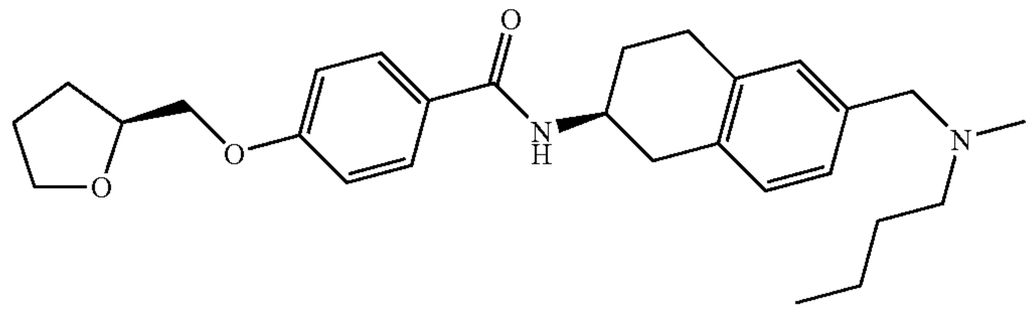
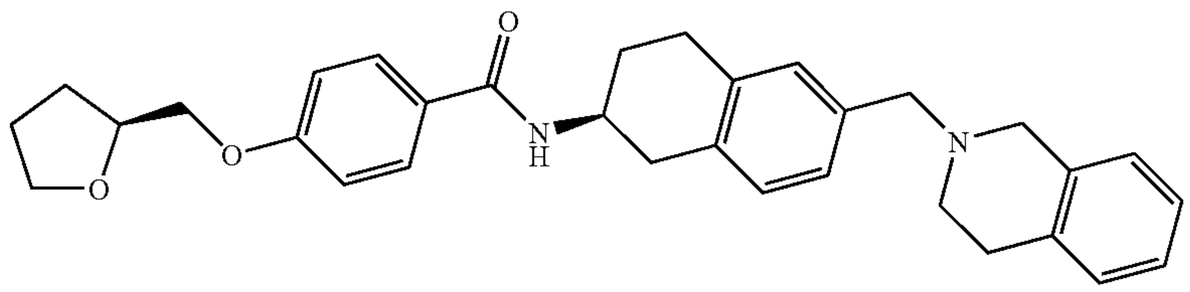
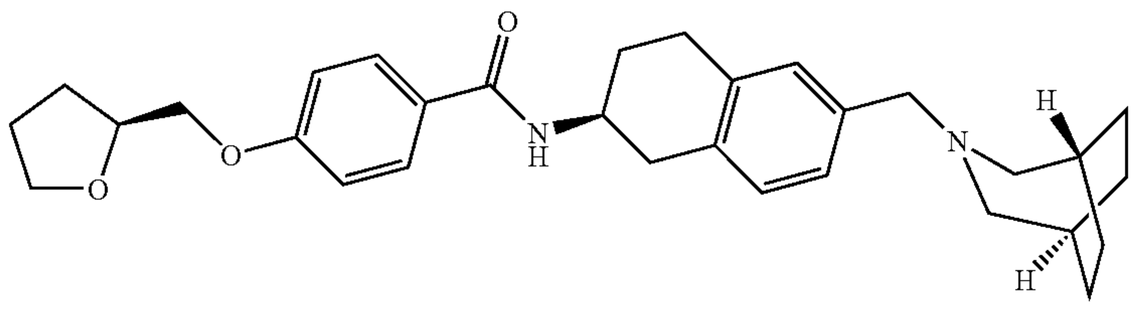
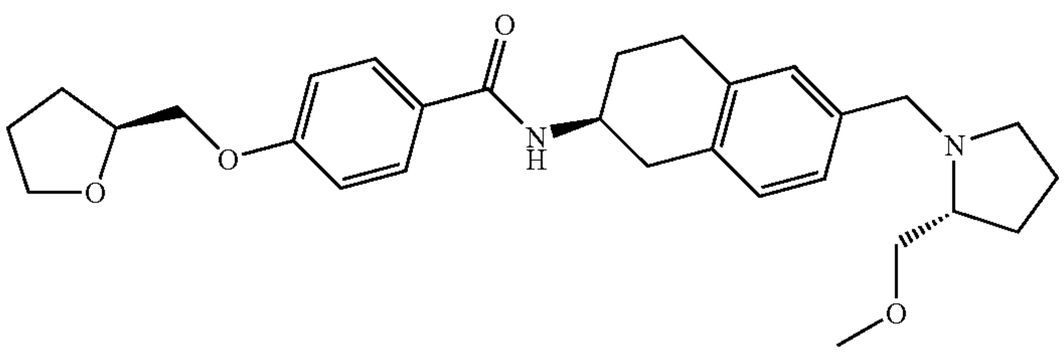
Ex. No.	Structure	Molecular-weight	ESI-MS $[M + H]^+$
3-43		464.60	465
3-44		491.63	492
3-45		462.63	463
3-46		450.62	451
3-47		496.65	497
3-48		488.67	489
3-49		478.63	479

TABLE 1-continued

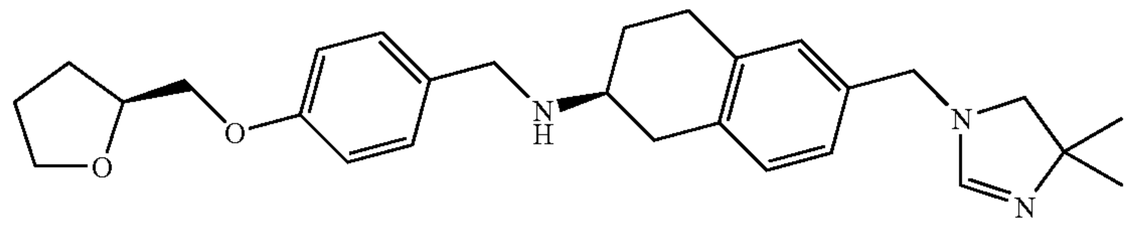
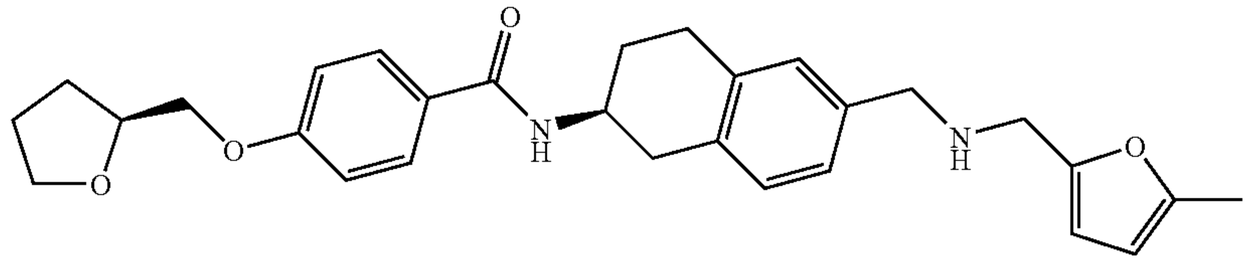
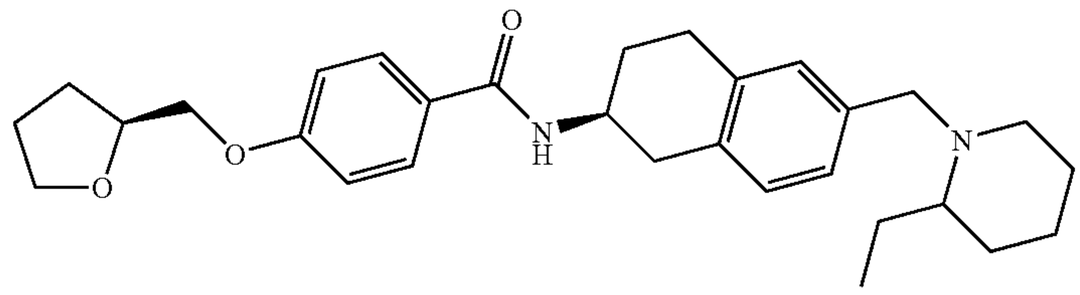
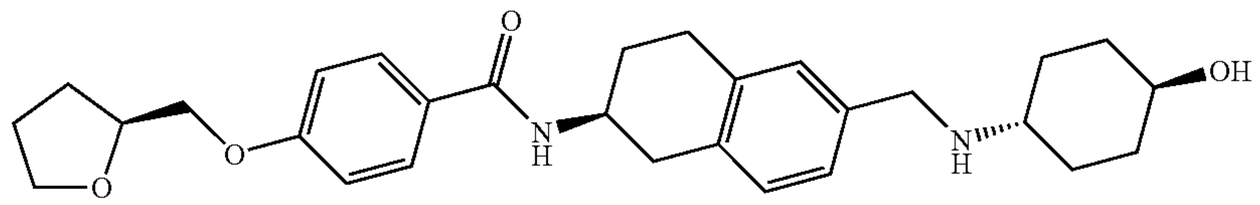
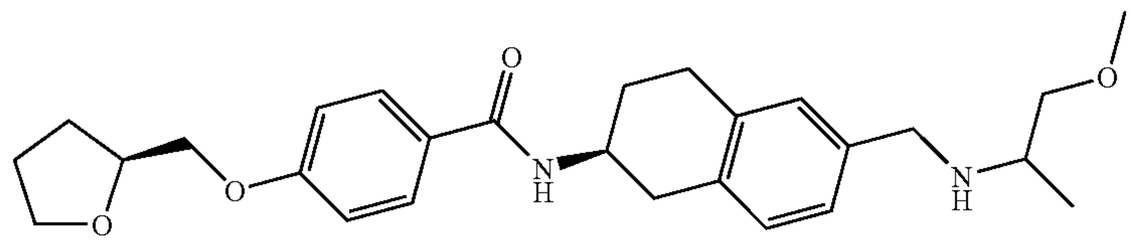
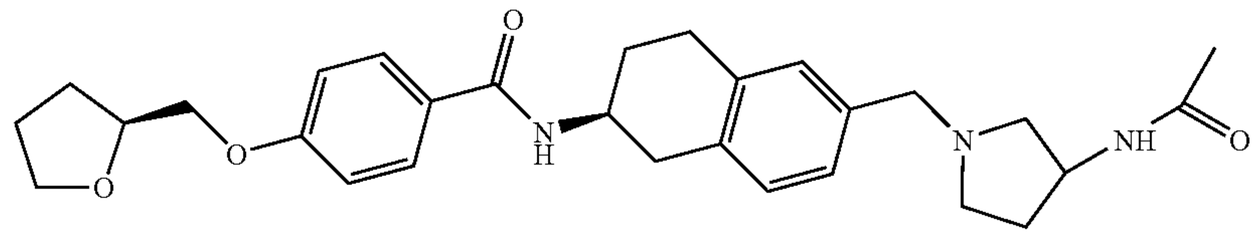
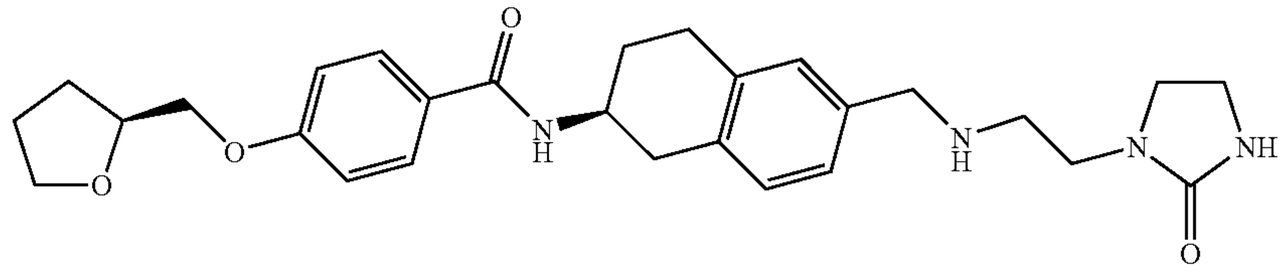
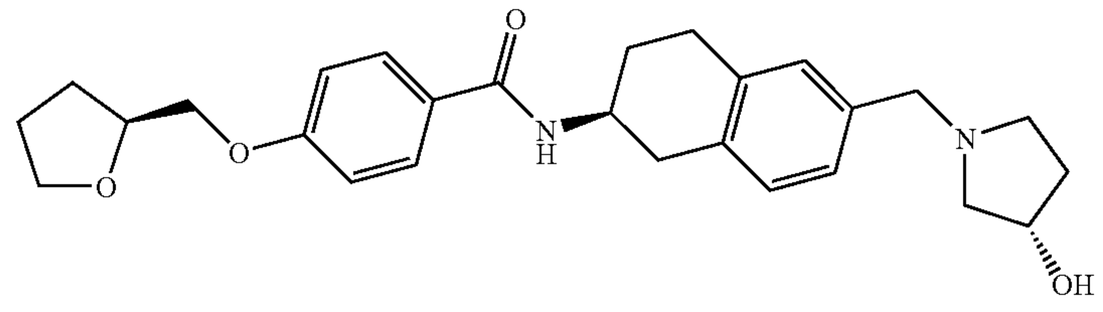
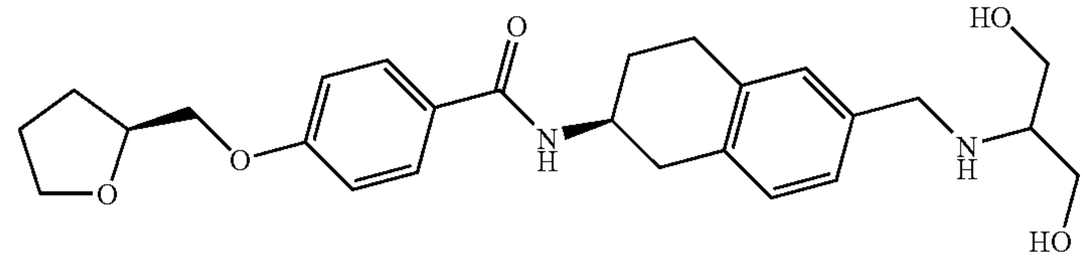
Ex. No.	Structure	Molecular-weight	ESI-MS $[M + H]^+$
3-50		461.60	462
3-51		474.60	475
3-52		476.66	477
3-53		478.63	479
3-54		452.59	453
3-55		491.63	492
3-56		492.62	493
3-57		450.58	451
3-58		454.56	455

TABLE 1-continued

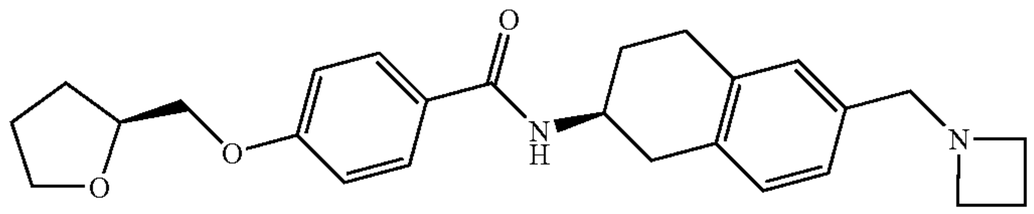
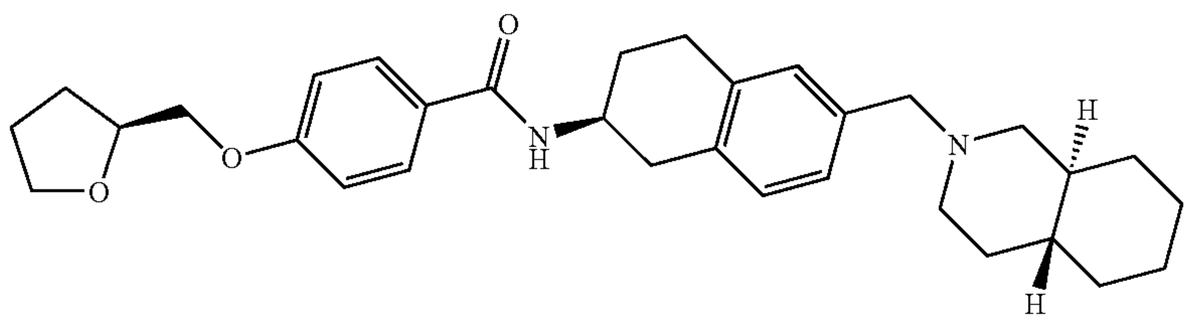
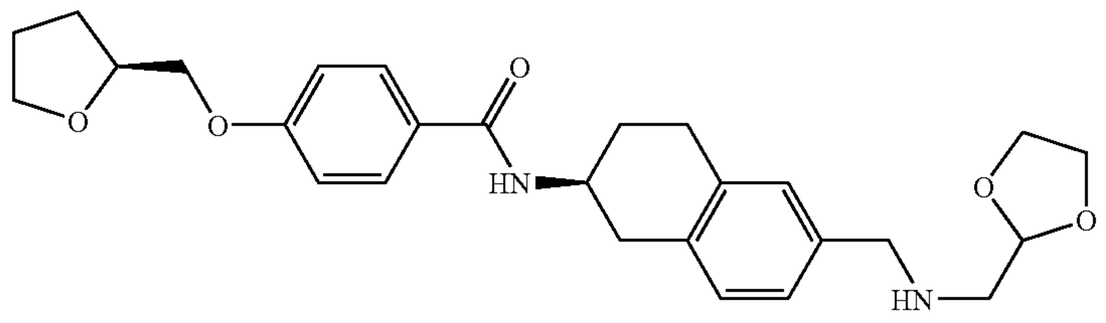
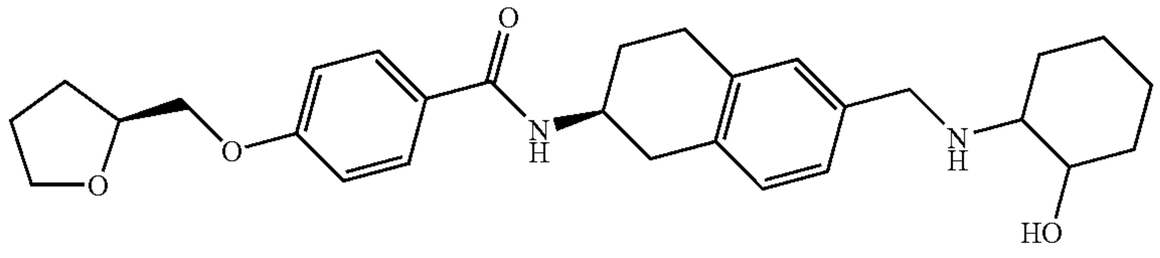
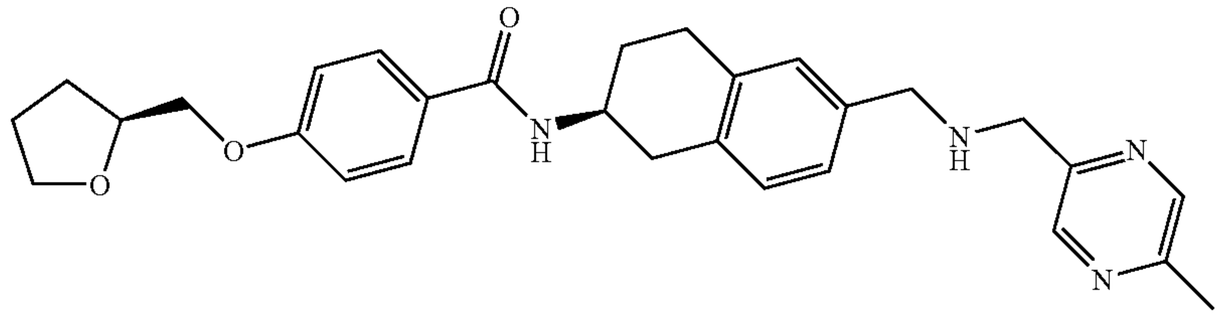
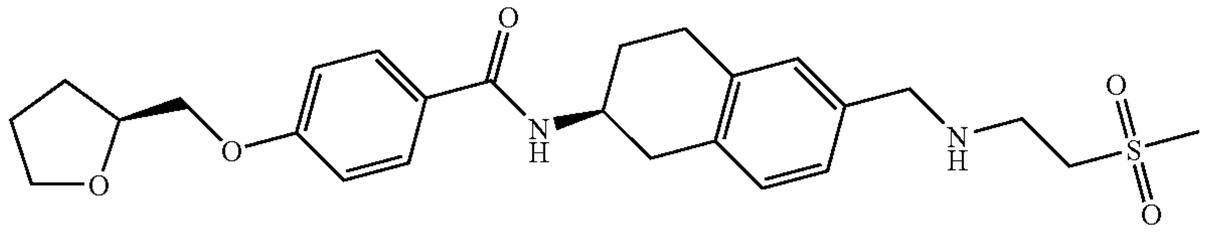
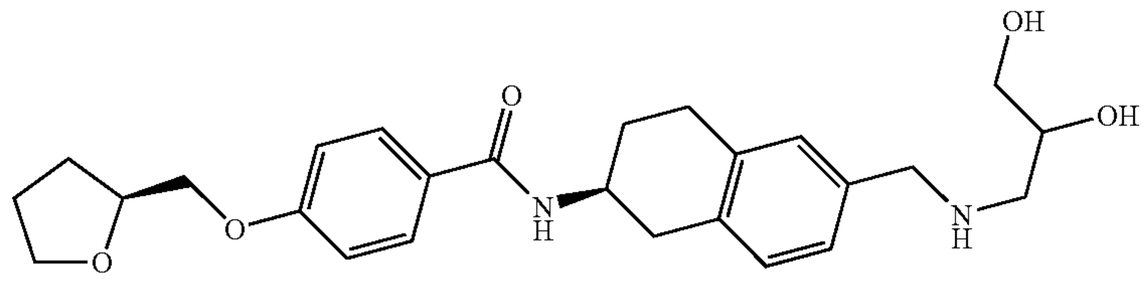
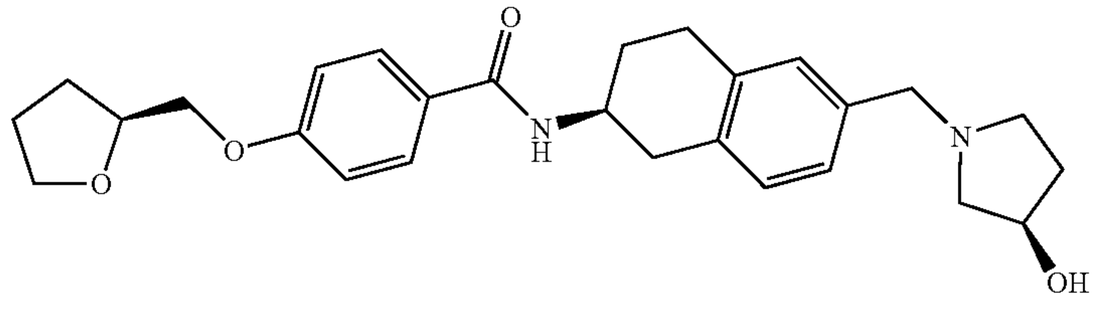
Ex. No.	Structure	Molecular-weight	ESI-MS $[M + H]^+$
3-59		420.55	421
3-60		502.70	503
3-61		466.58	467
3-62		478.63	479
3-63		486.61	487
3-64		486.63	487
3-65		454.56	455
3-66		450.58	451

TABLE 1-continued

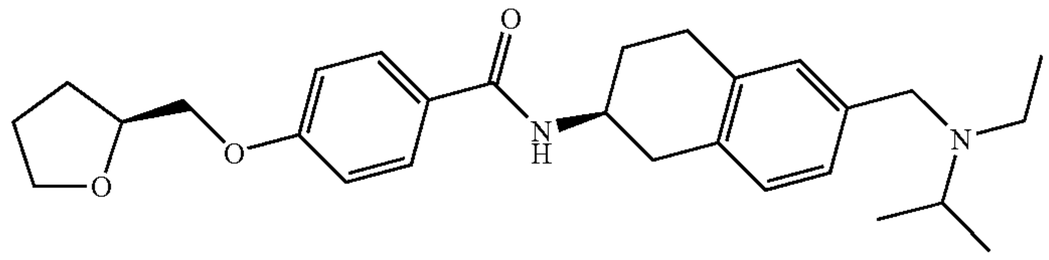
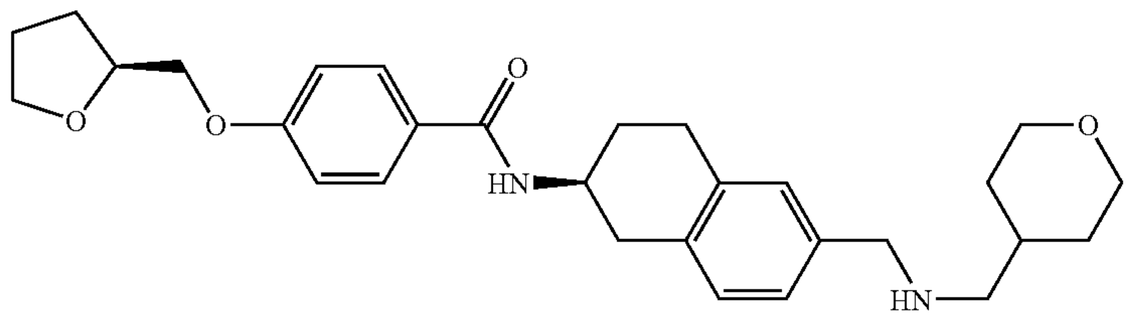
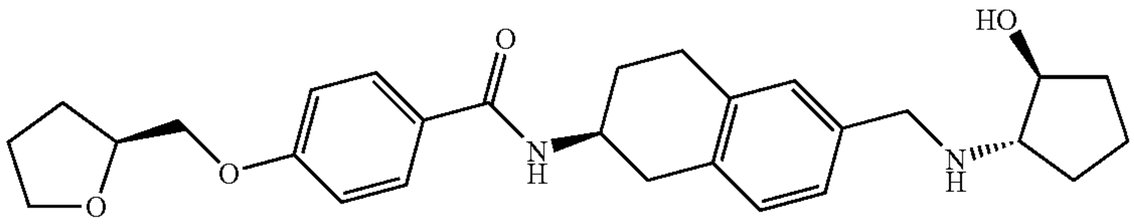
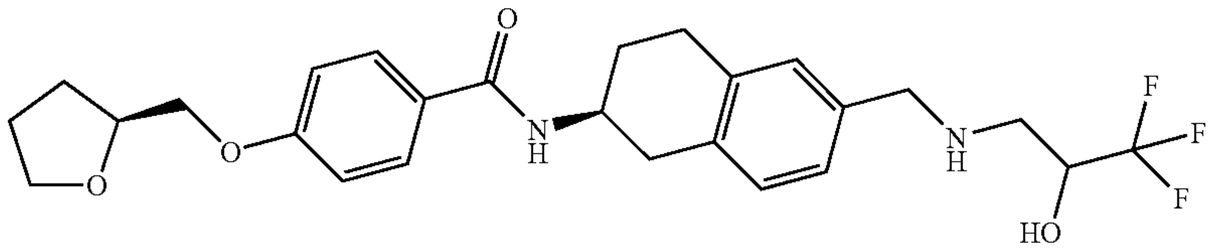
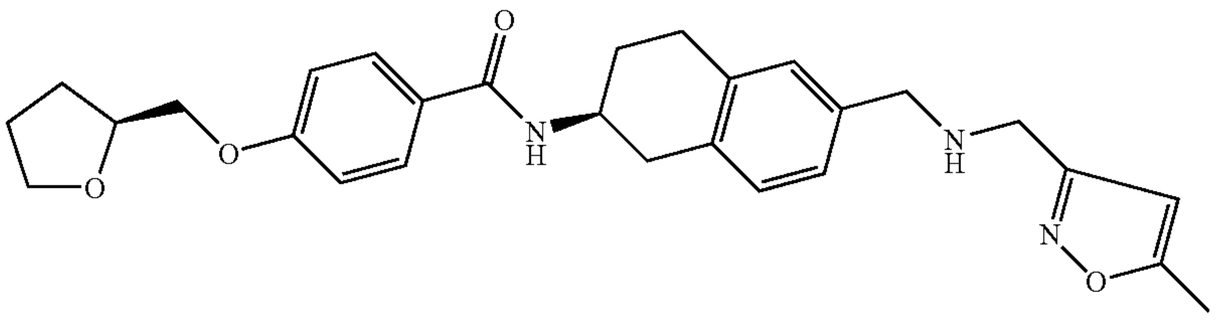
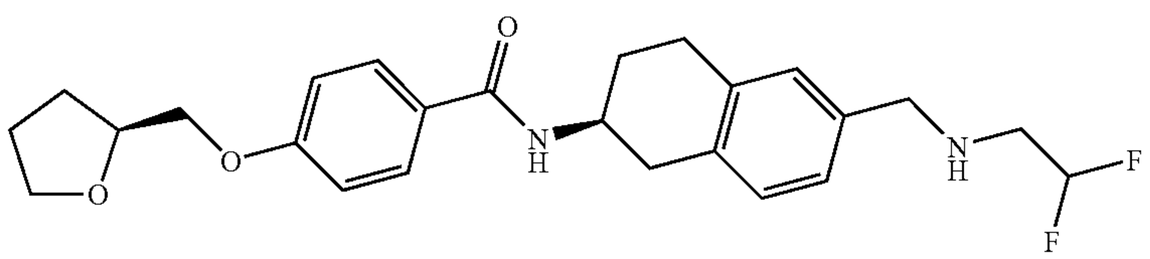
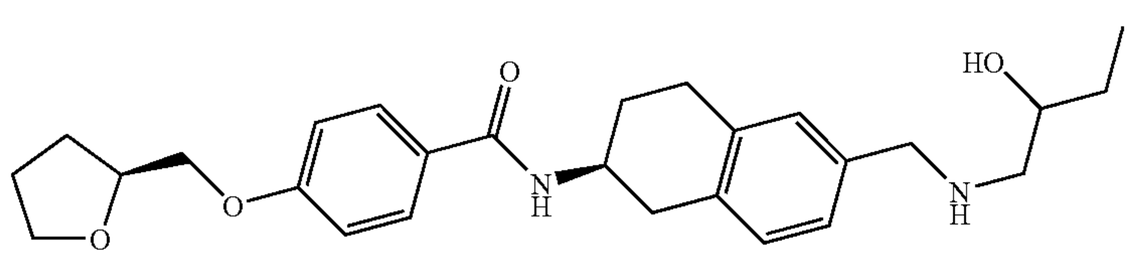
Ex. No.	Structure	Molecular-weight	ESI-MS $[M + H]^+$
3-67		450.62	451
3-68		478.63	479
3-69		464.60	465
3-70		492.54	493
3-71		475.59	476
3-72		463.58	464
3-73		444.52	445
3-74		452.59	453

TABLE 1-continued

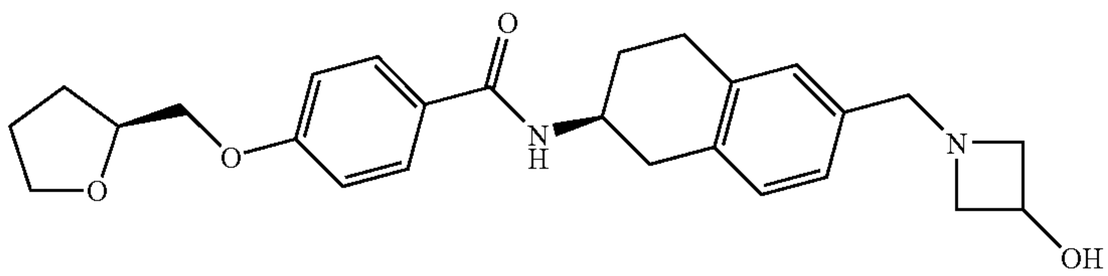
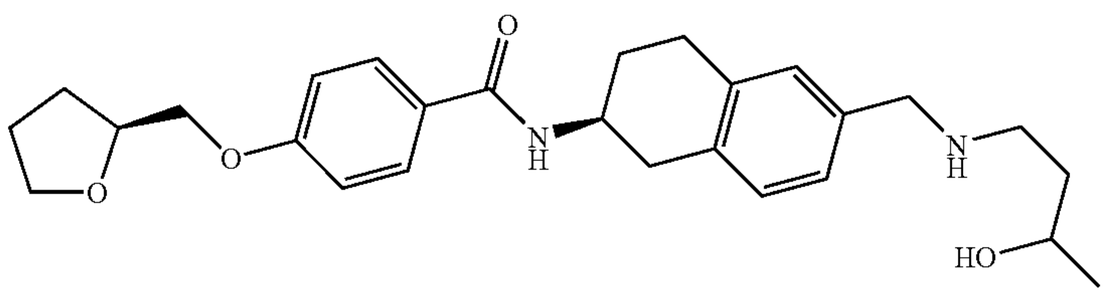
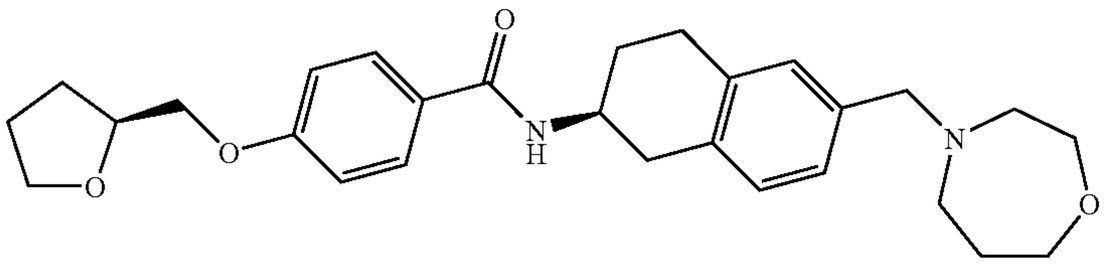
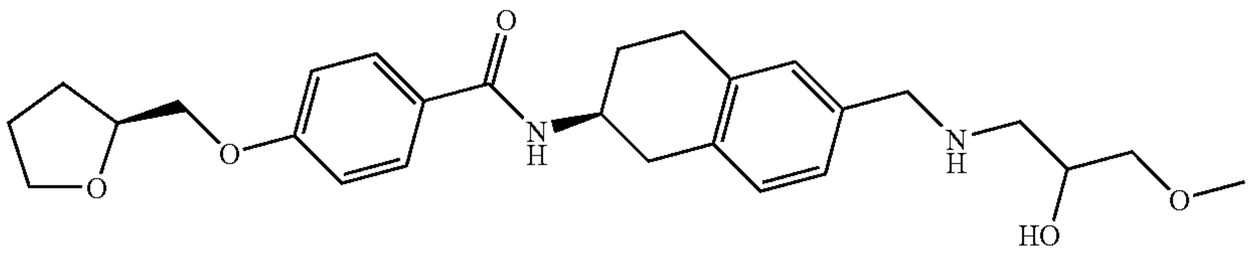
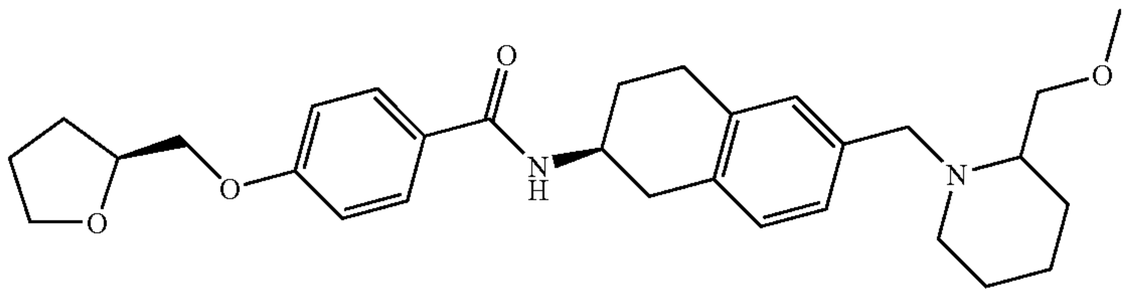
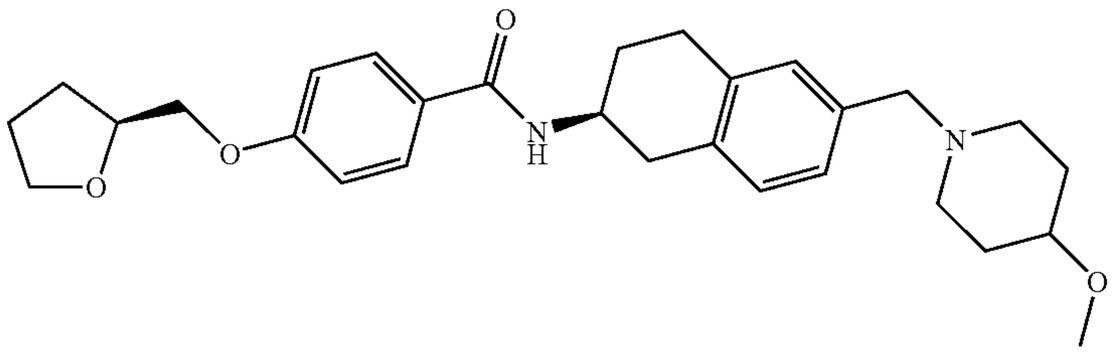
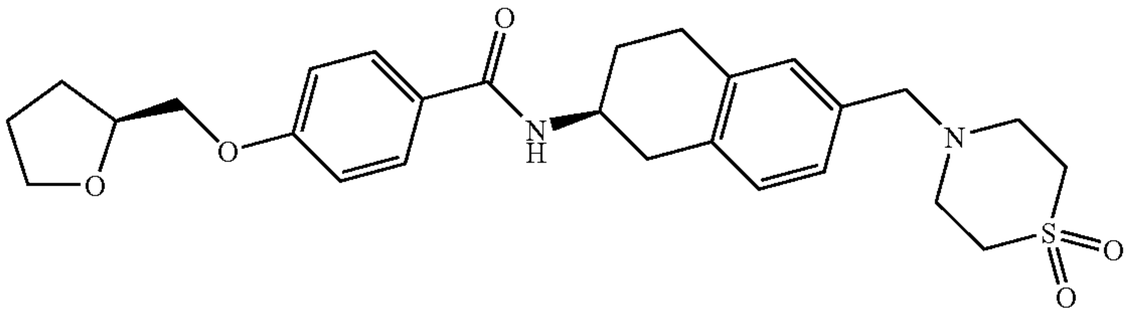
Ex. No.	Structure	Molecular-weight	ESI-MS $[M + H]^+$
3-75		436.55	437
3-76		452.59	453
3-77		464.60	465
3-78		468.59	469
3-79		492.66	493
3-80		478.63	479
3-81		498.64	499

TABLE 1-continued

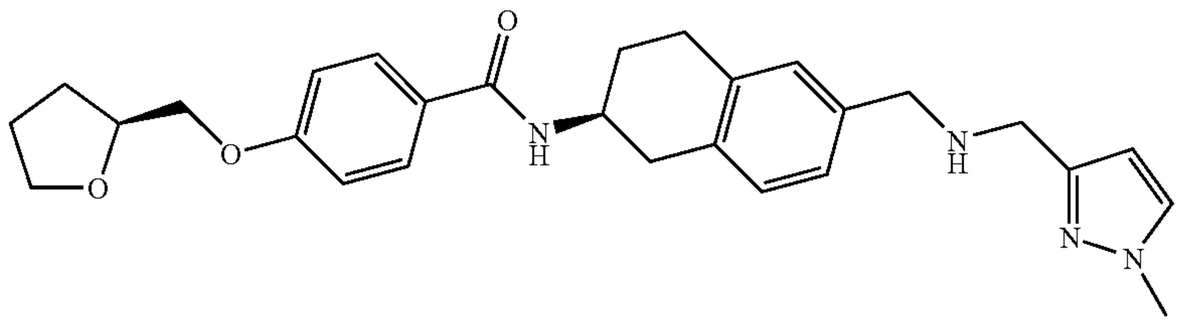
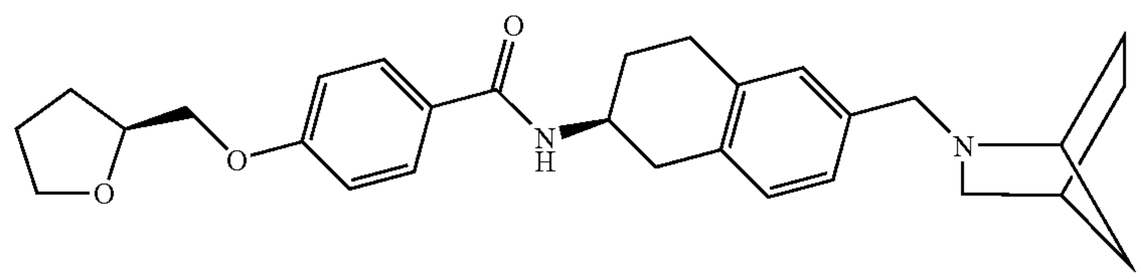
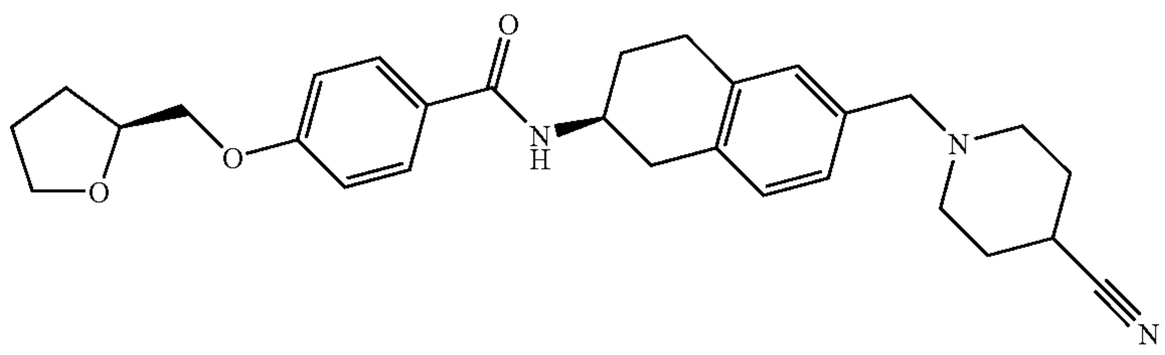
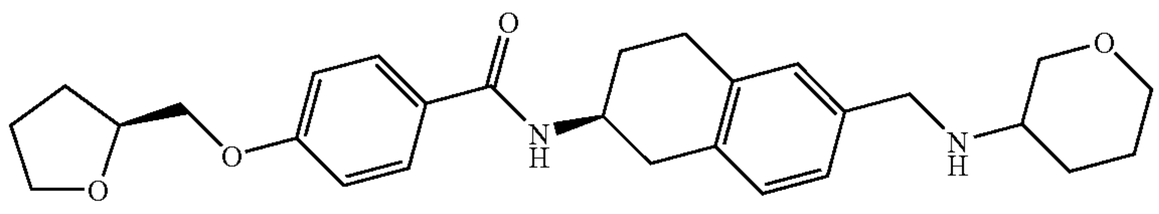
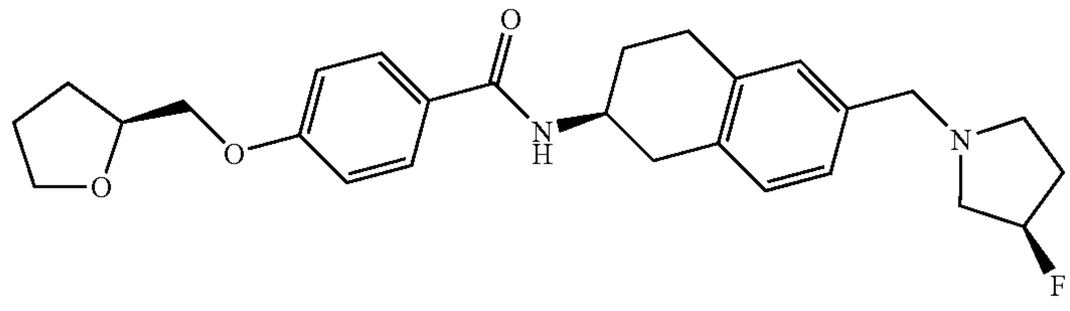
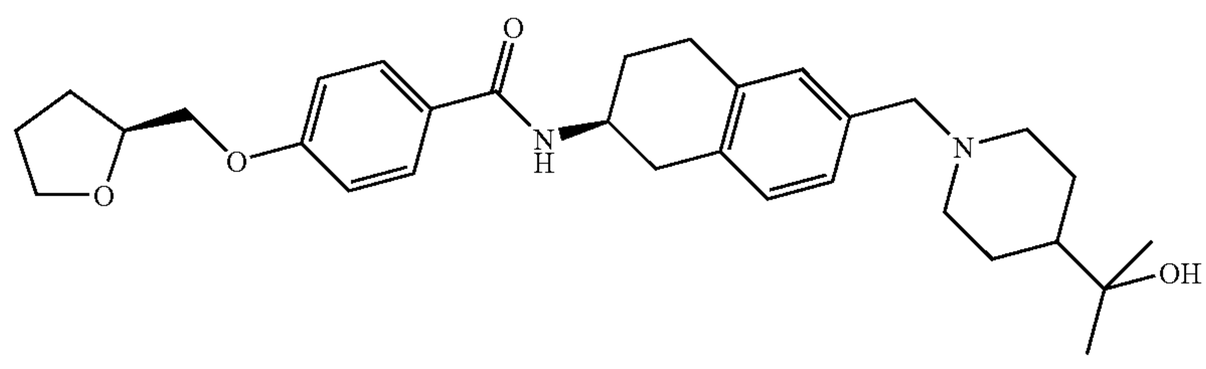
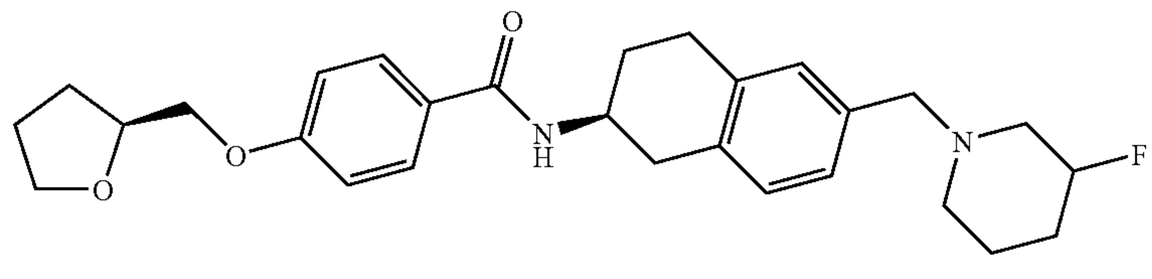
Ex. No.	Structure	Molecular-weight	ESI-MS $[M + H]^+$
3-82		474.60	475
3-83		460.61	461
3-84		473.61	474
3-85		464.60	465
3-86		452.57	453
3-87		478.63	479
3-88		506.68	507
3-89		466.59	467

TABLE 1-continued

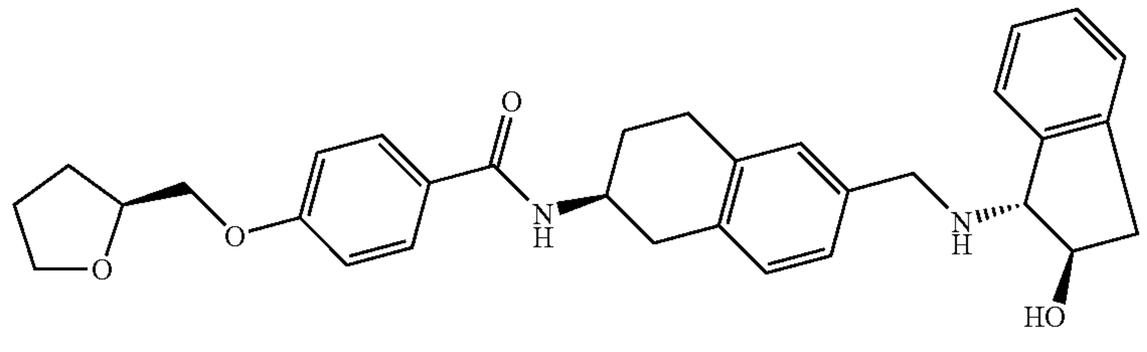
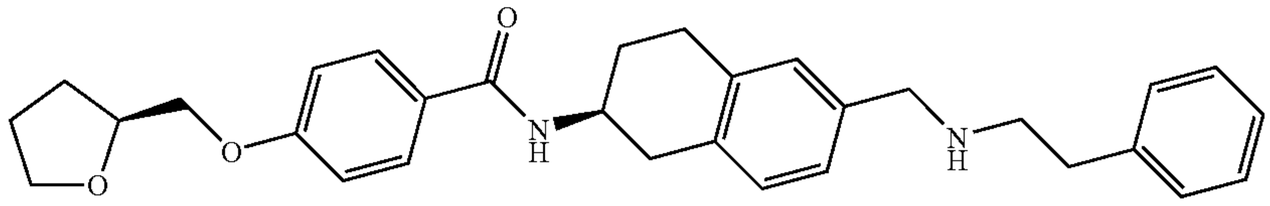
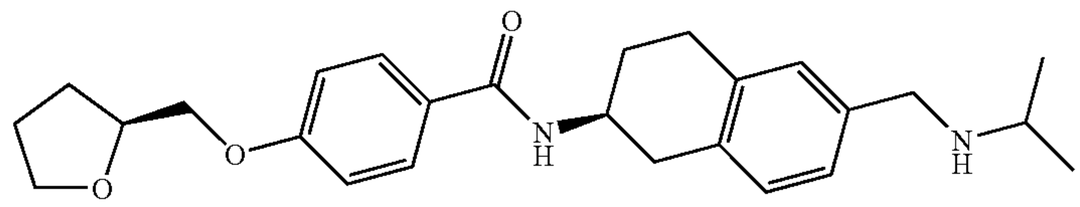
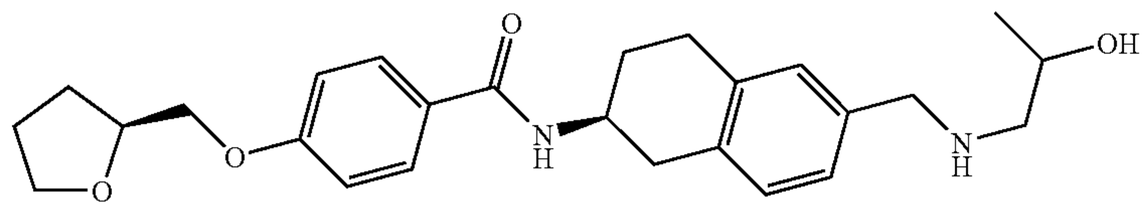
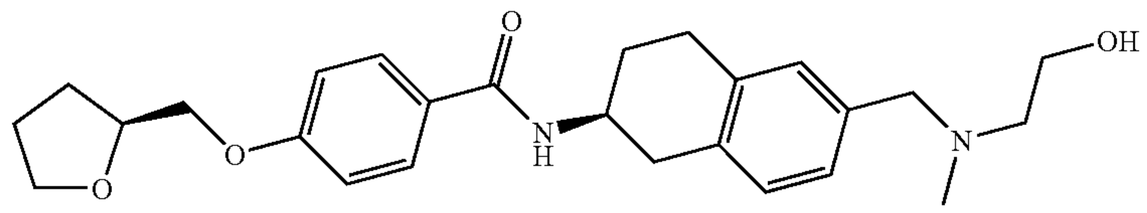
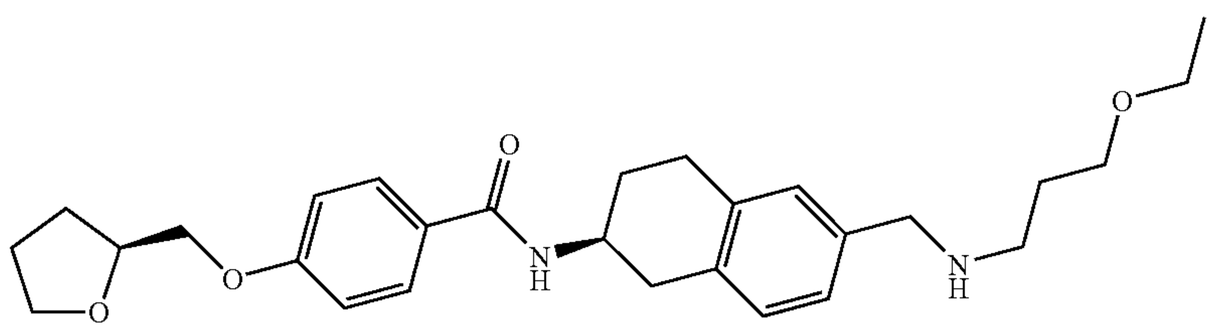
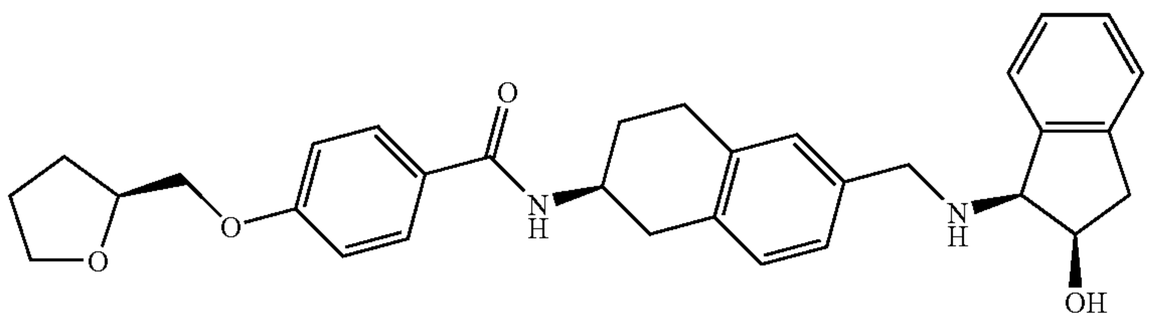
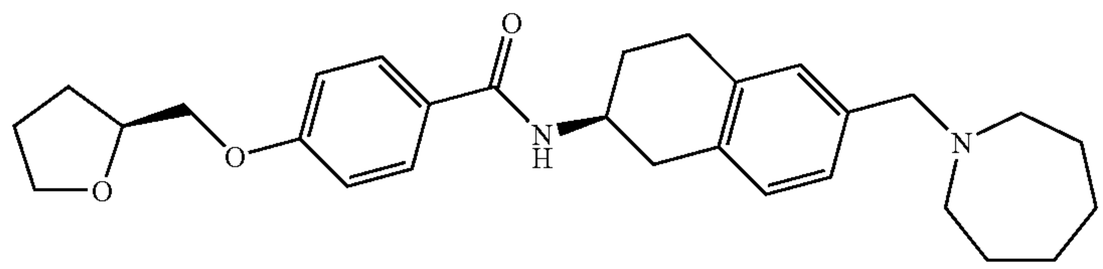
Ex. No.	Structure	Molecular-weight	ESI-MS $[M + H]^+$
3-90		512.65	513
3-91		484.64	485
3-92		422.57	423
3-93		438.57	439
3-94		438.57	439
3-95		466.62	467
3-96		512.65	513
3-97		462.63	463

TABLE 1-continued

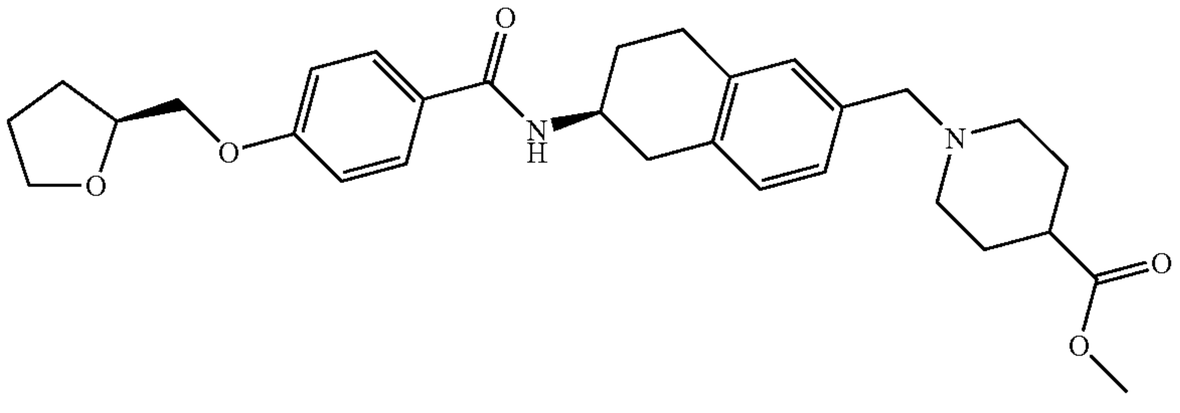
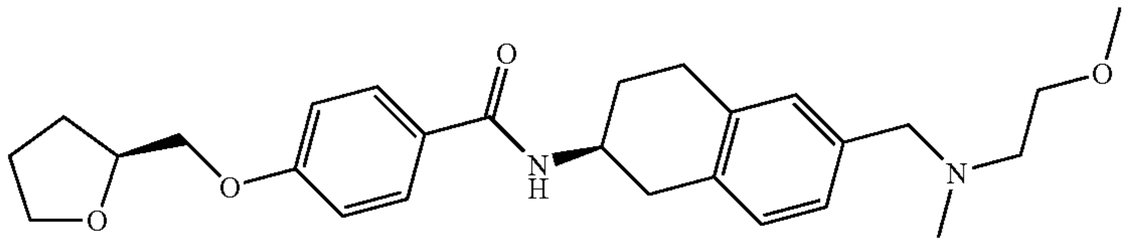
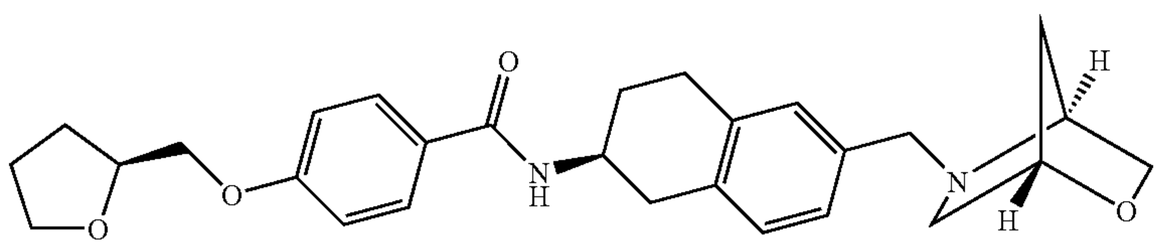
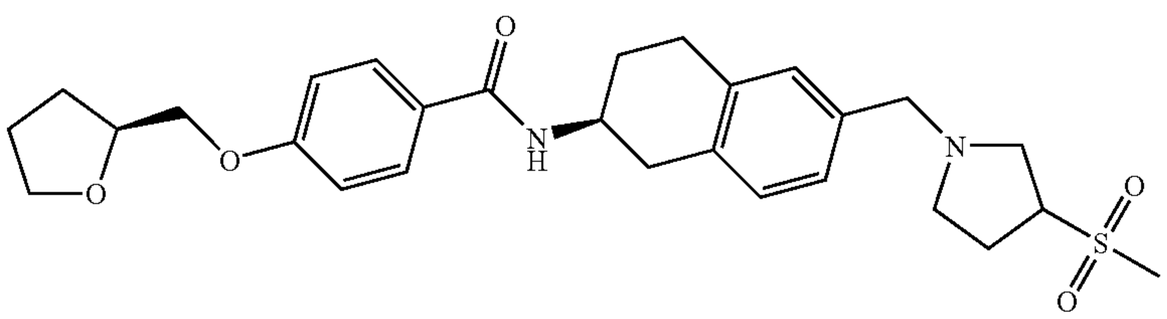
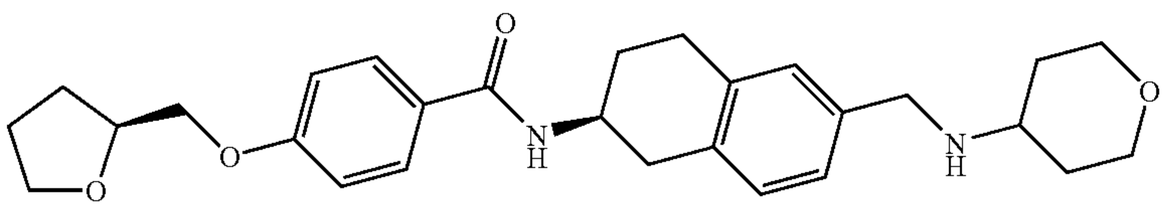
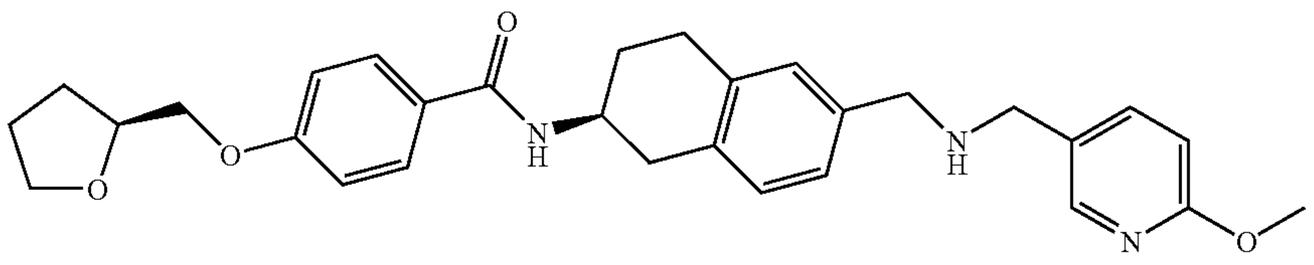
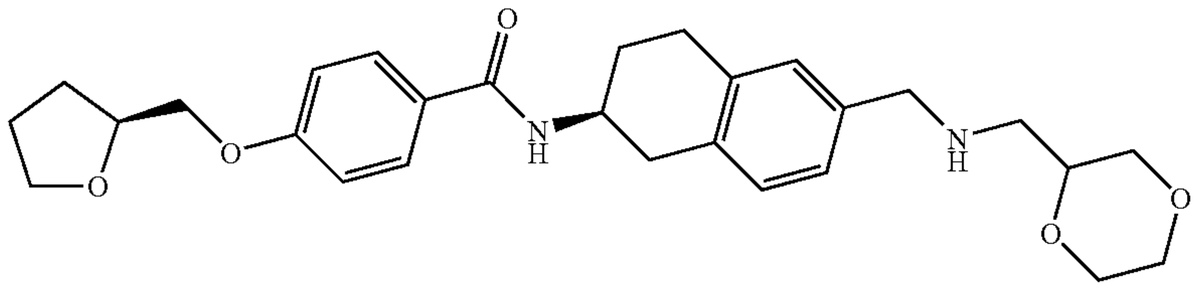
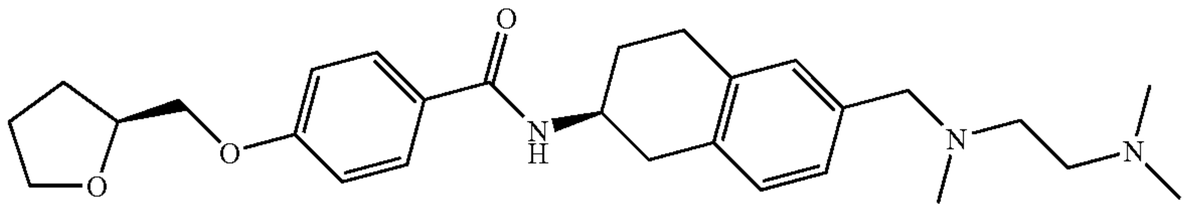
Ex. No.	Structure	Molecular-weight	ESI-MS $[M + H]^+$
3-98		506.64	507
3-99		452.59	453
3-100		462.59	463
3-101		512.67	513
3-102		464.60	465
3-103		501.62	502
3-104		480.60	481
3-105		465.63	466

TABLE 1-continued

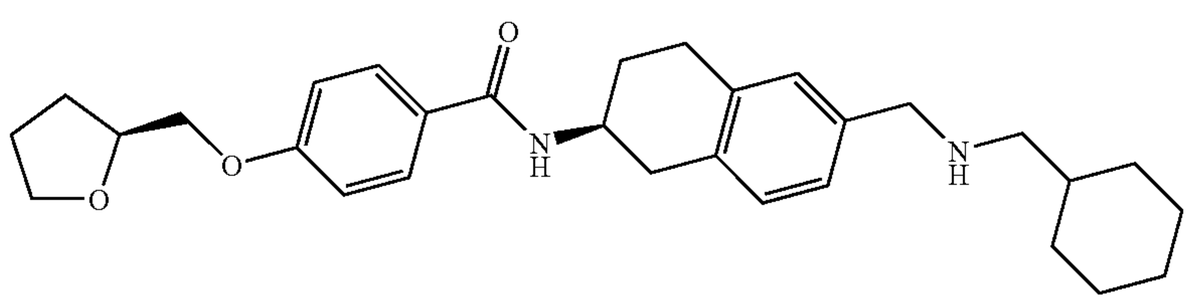
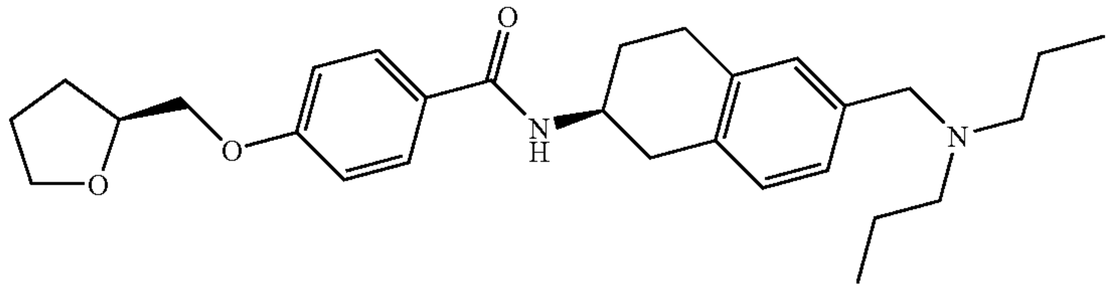
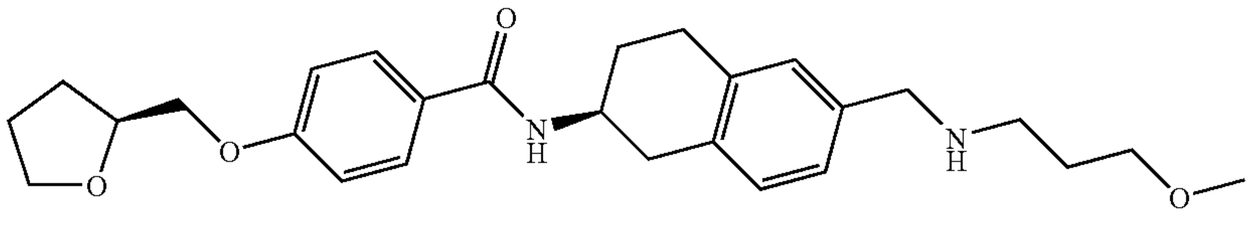
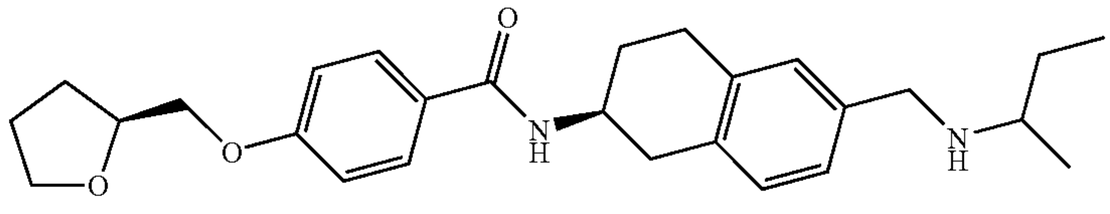
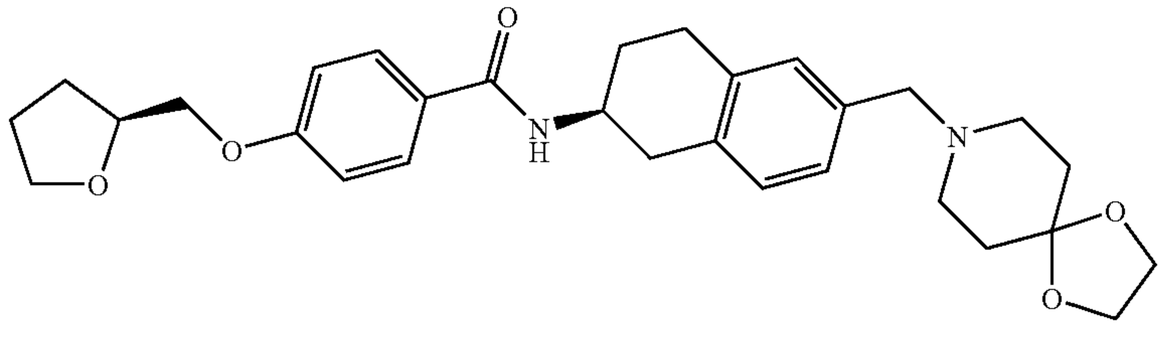
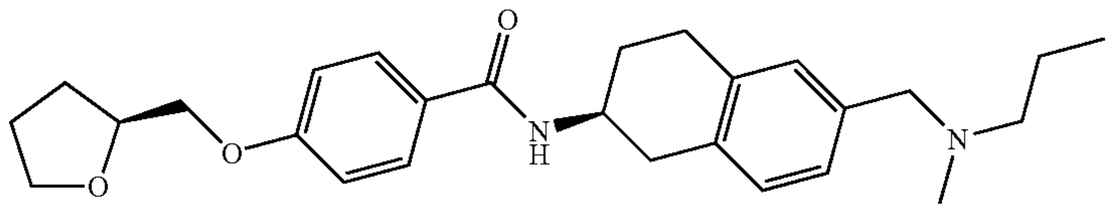
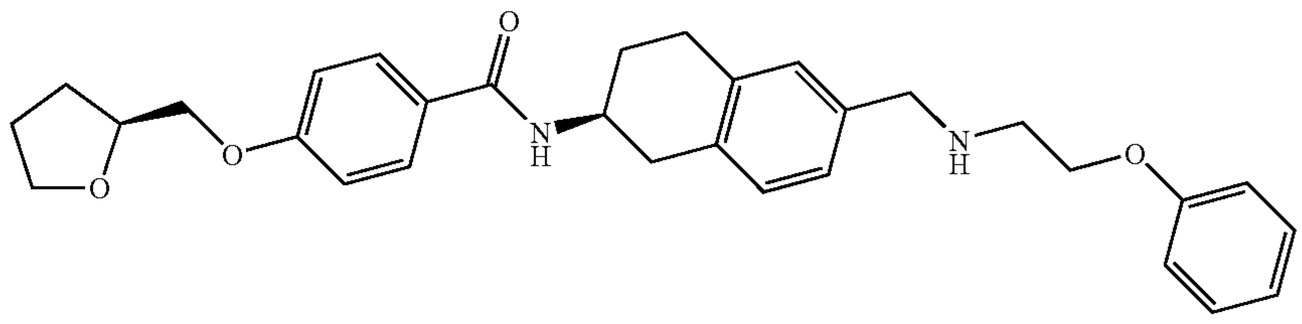
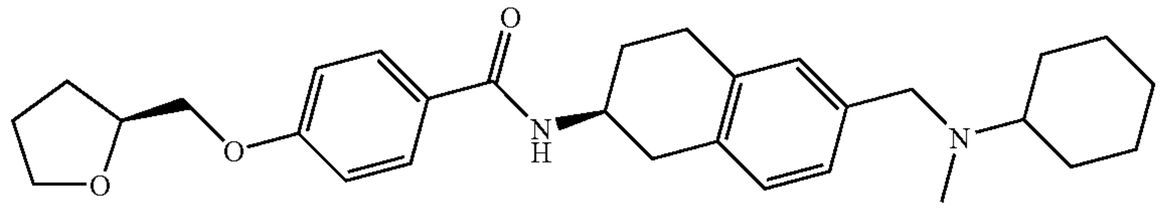
Ex. No.	Structure	Molecular-weight	ESI-MS $[M + H]^+$
3-106		476.66	477
3-107		464.65	465
3-108		452.59	453
3-109		436.59	437
3-110		506.64	507
3-111		436.59	437
3-112		500.64	501
3-113		476.66	477

TABLE 1-continued

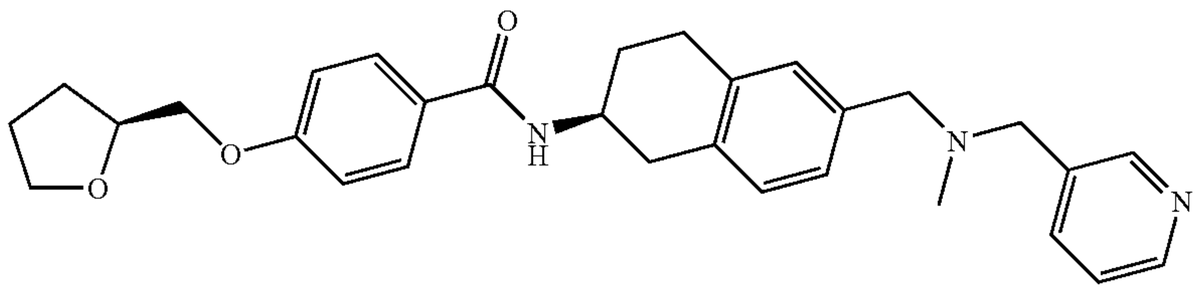
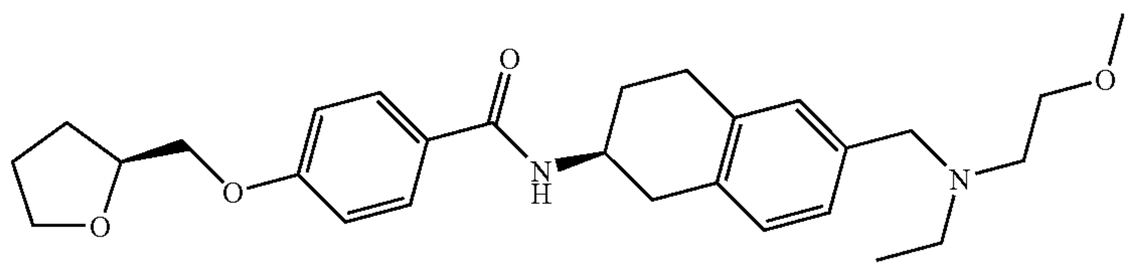
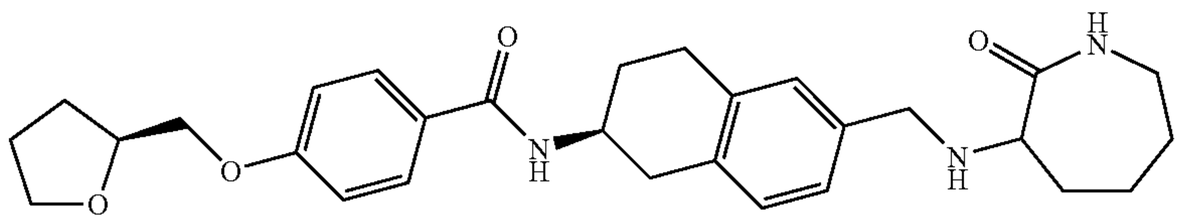
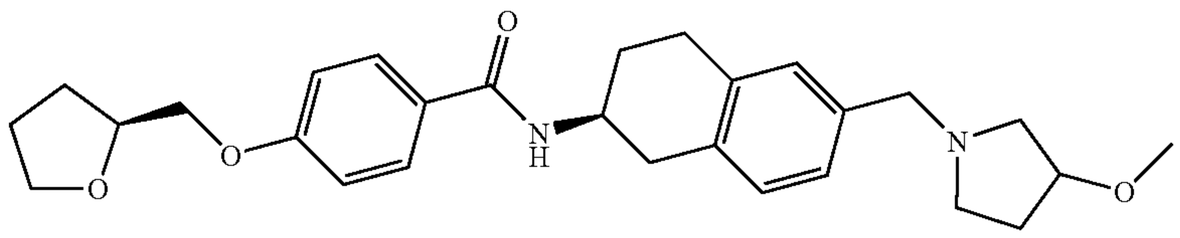
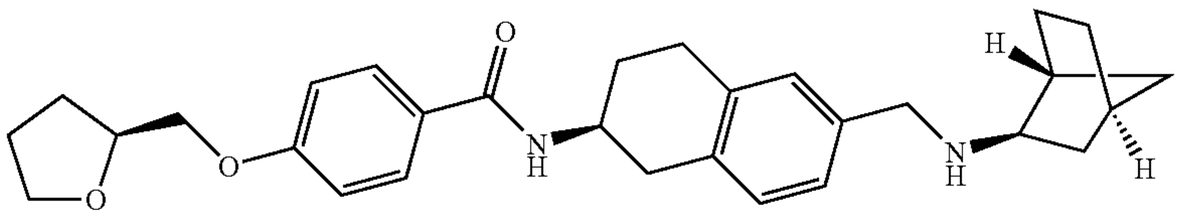
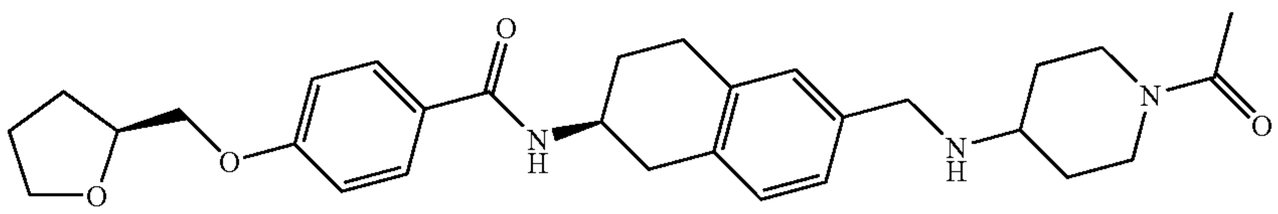
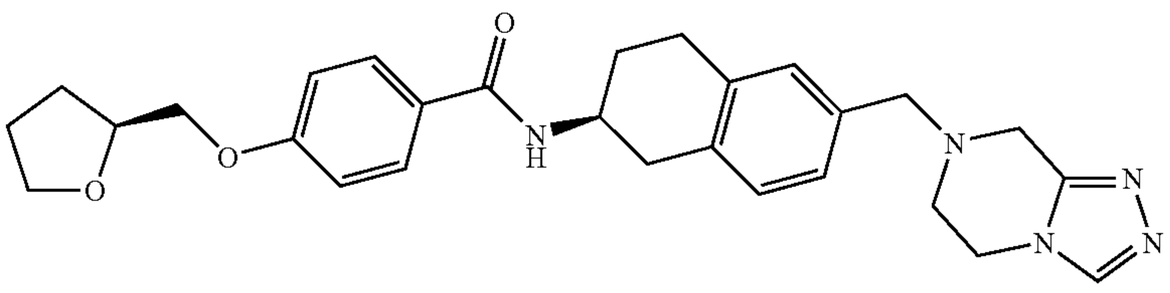
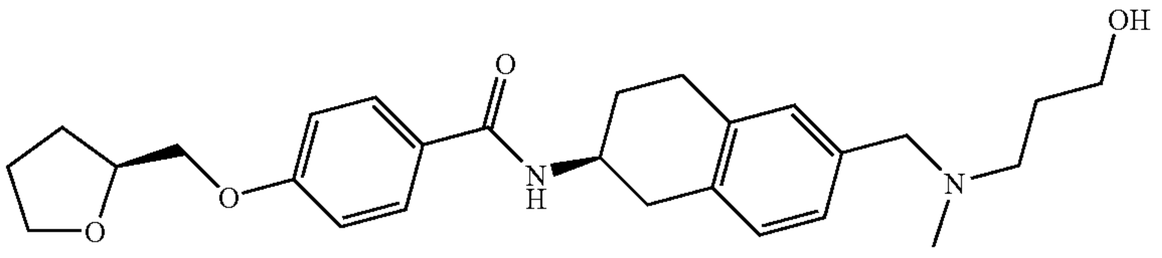
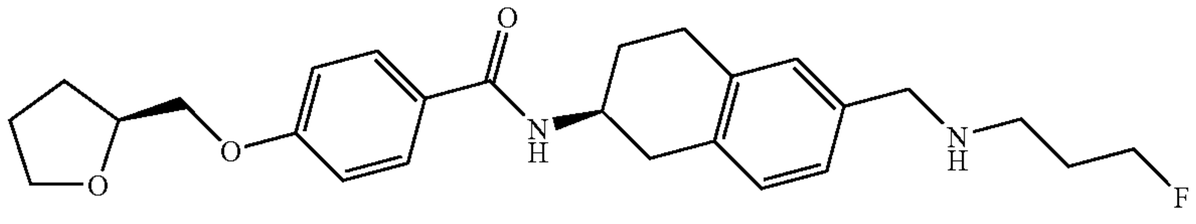
Ex. No.	Structure	Molecular-weight	ESI-MS $[M + H]^+$
3-114		485.63	486
3-115		466.62	467
3-116		491.63	492
3-117		464.60	465
3-118		474.64	475
3-119		505.66	506
3-120		487.60	488
3-121		452.59	453
3-122		440.56	441

TABLE 1-continued

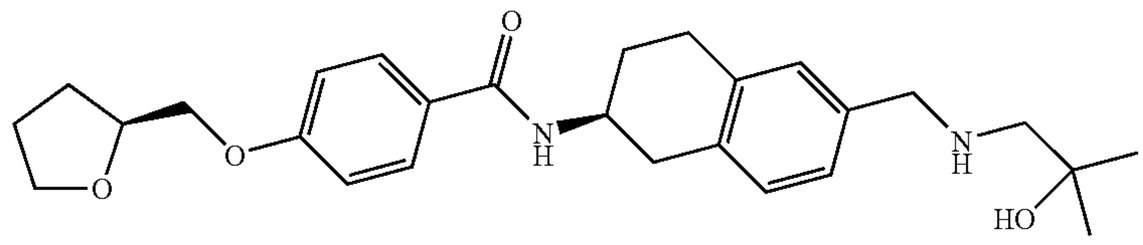
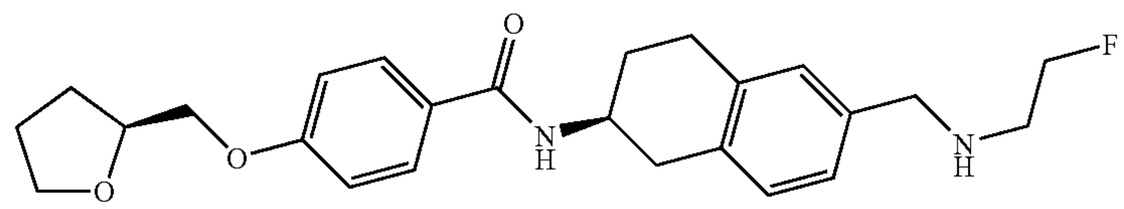
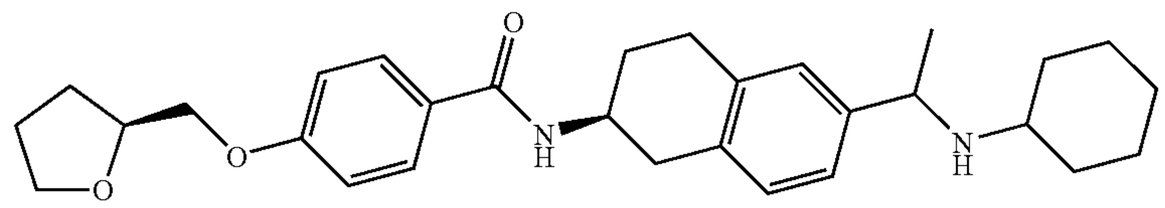
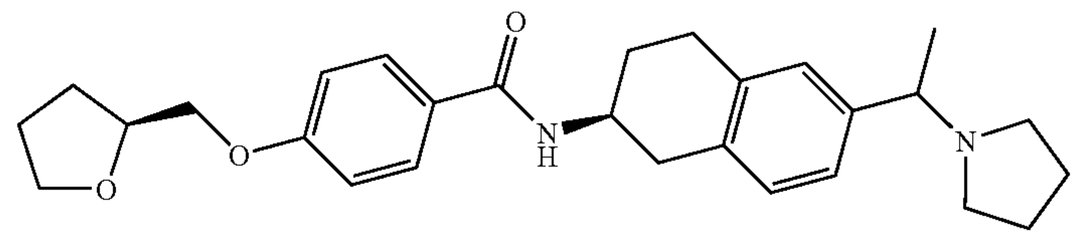
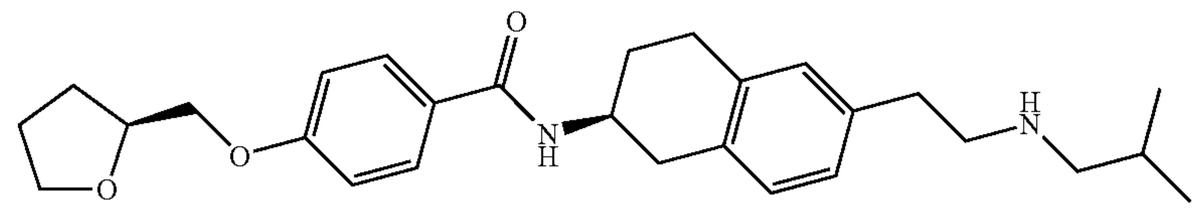
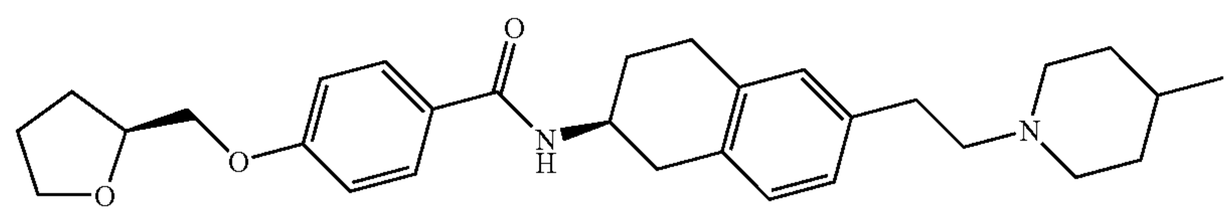
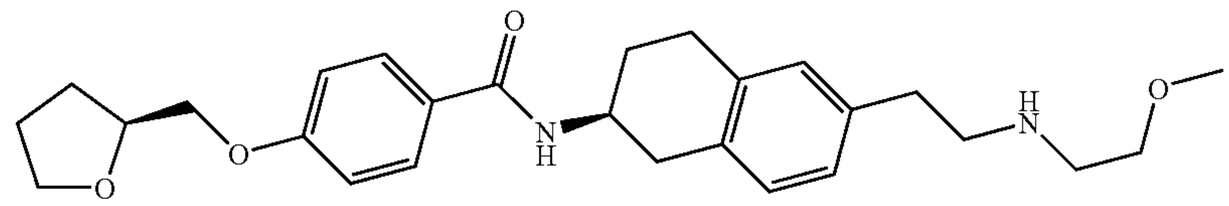
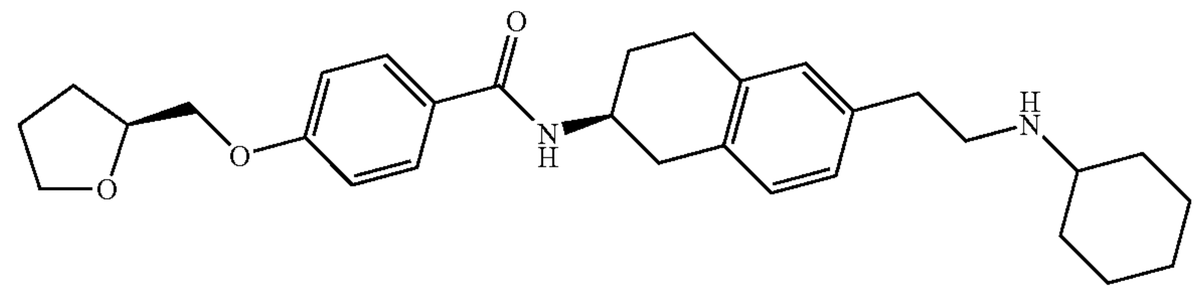
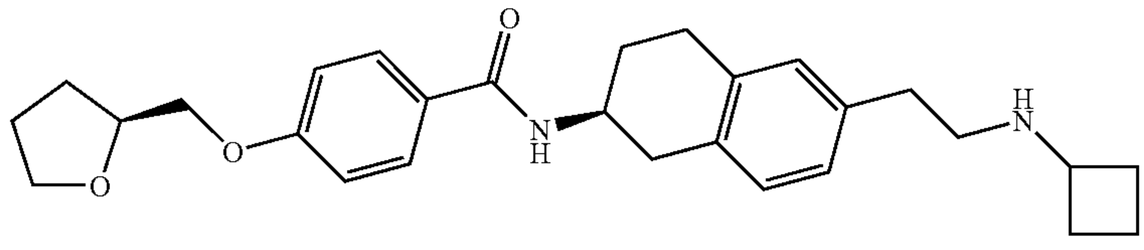
Ex. No.	Structure	Molecular-weight	ESI-MS $[M + H]^+$
3-123		452.59	453
3-124		426.53	427
3-125		476.66	477
3-126		448.60	449
3-127		450.62	451
3-128		476.66	477
3-129		452.59	453
3-130		476.66	477
3-131		448.60	449

TABLE 1-continued

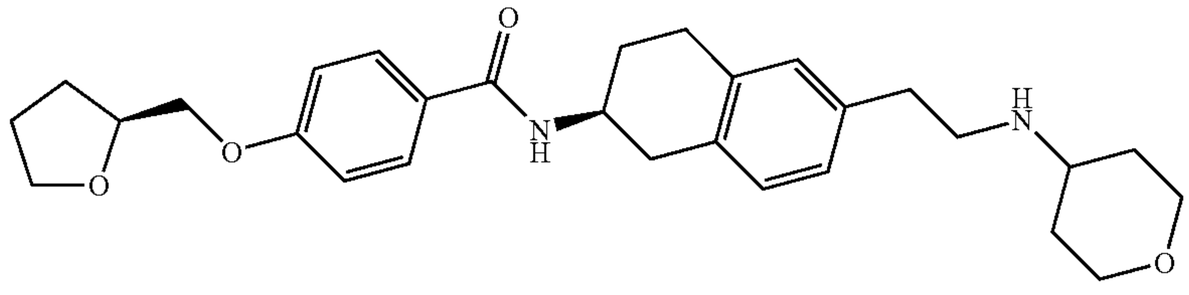
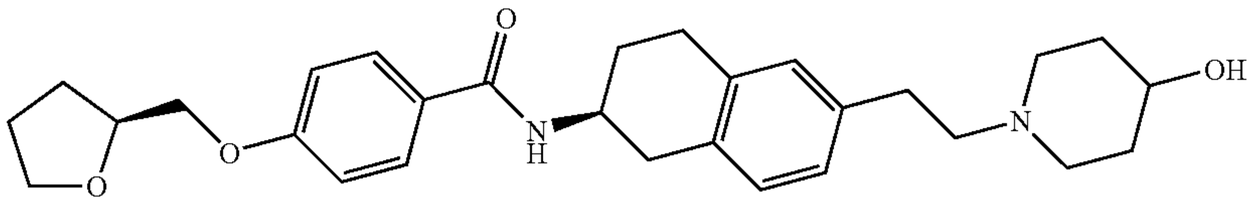
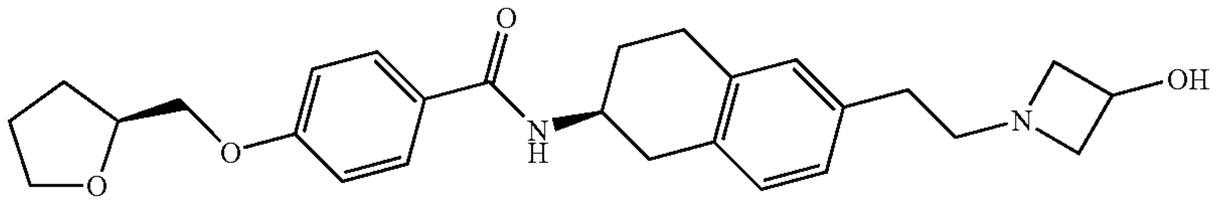
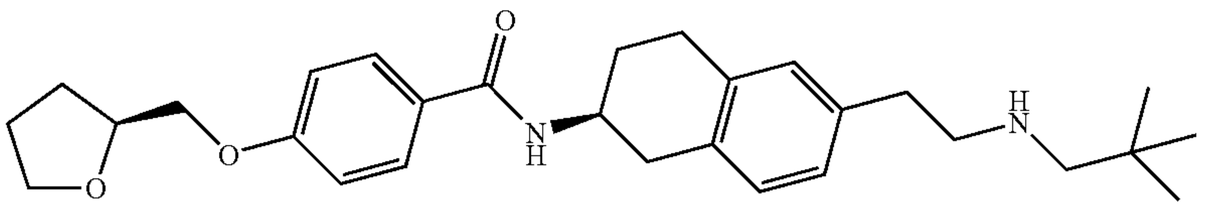
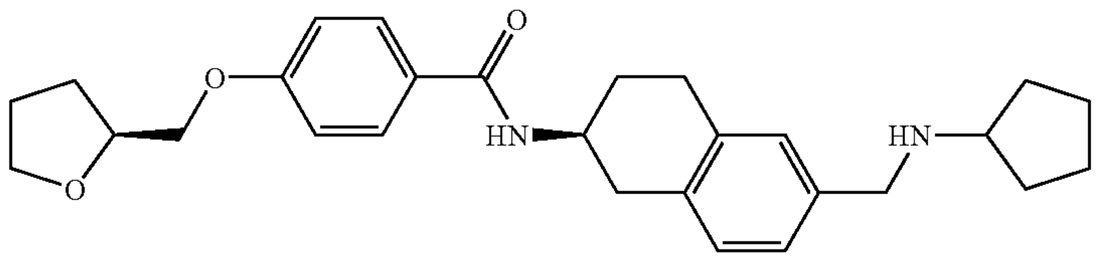
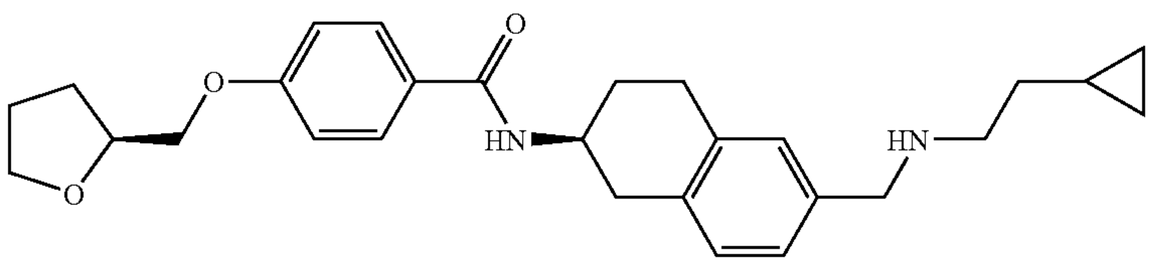
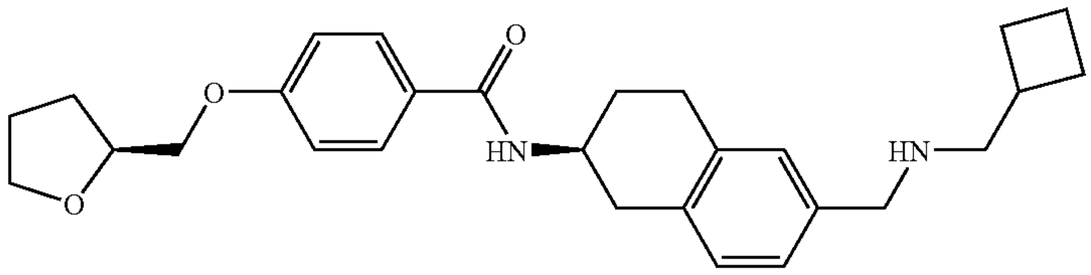
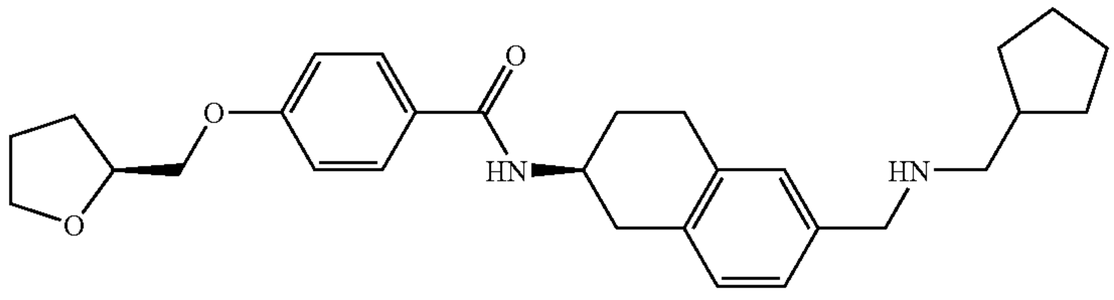
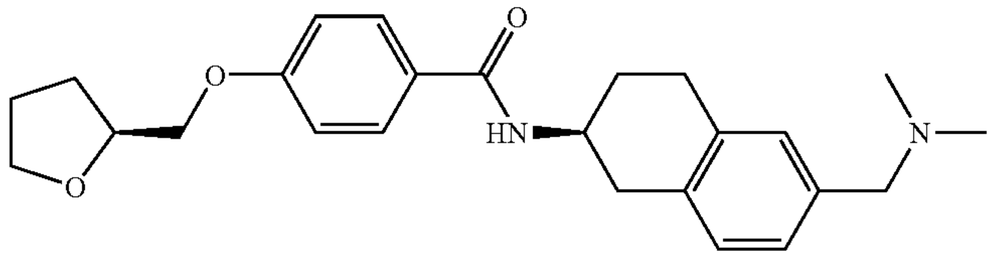
Ex. No.	Structure	Molecular-weight	ESI-MS $[M + H]^+$
3-132		478.63	479
3-133		478.63	479
3-134		450.58	451
3-135		464.65	465
3-136		448.60	449
3-137		448.60	449
3-138		448.60	449
3-139		462.63	463
3-140		408.54	409

TABLE 1-continued

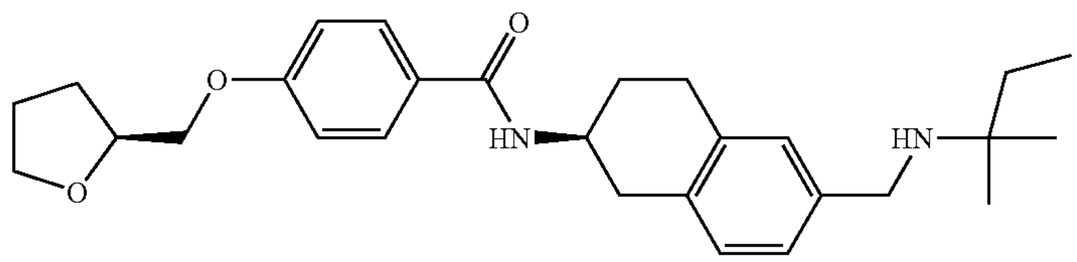
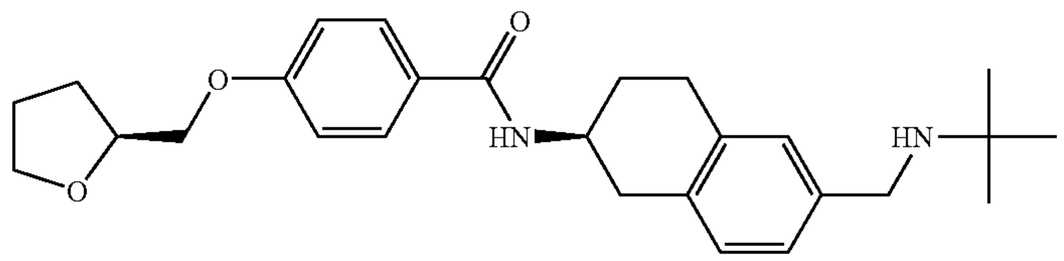
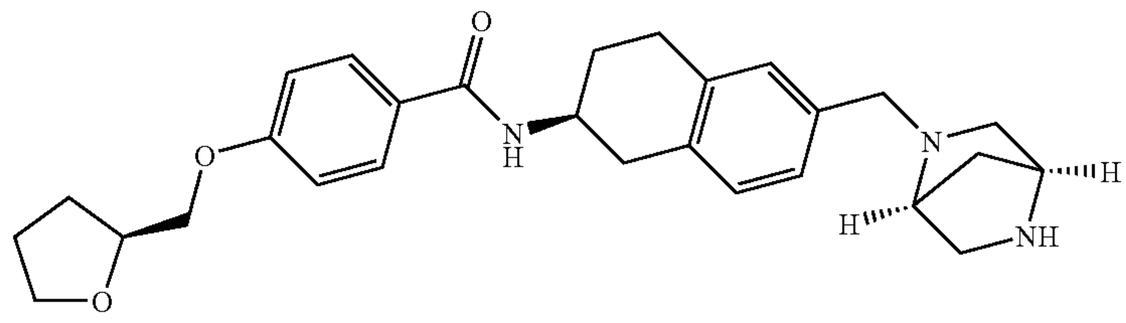
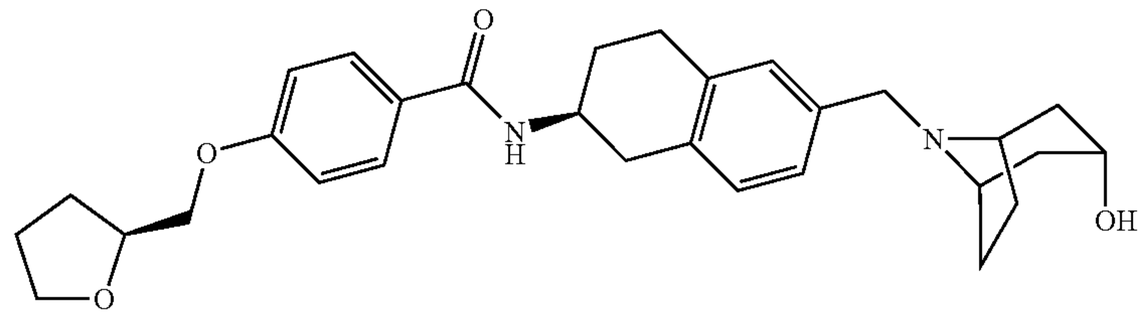
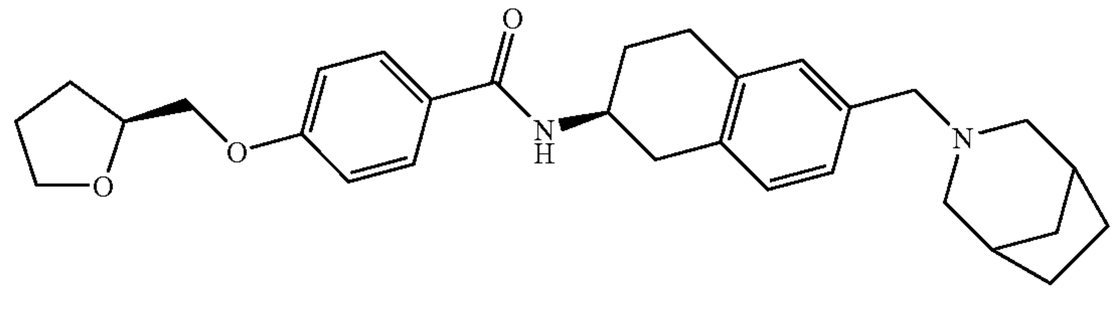
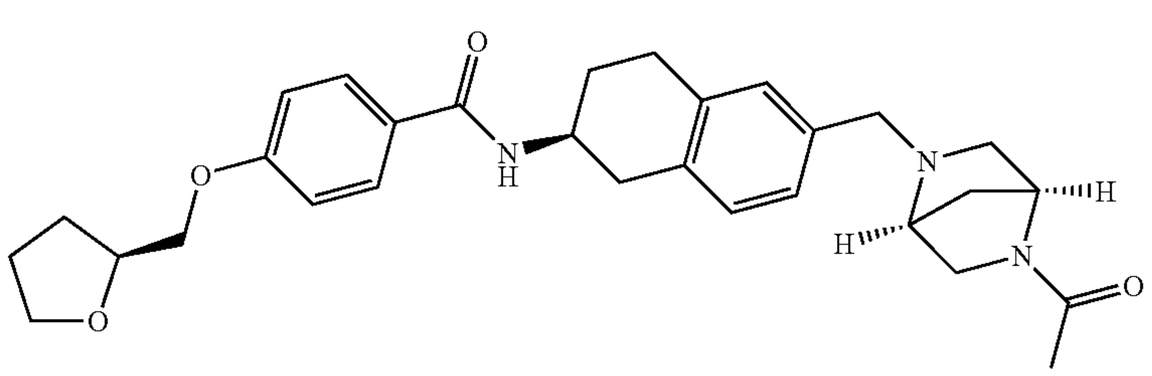
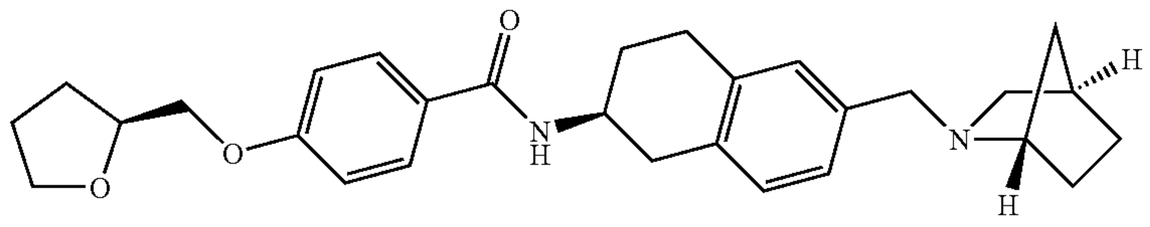
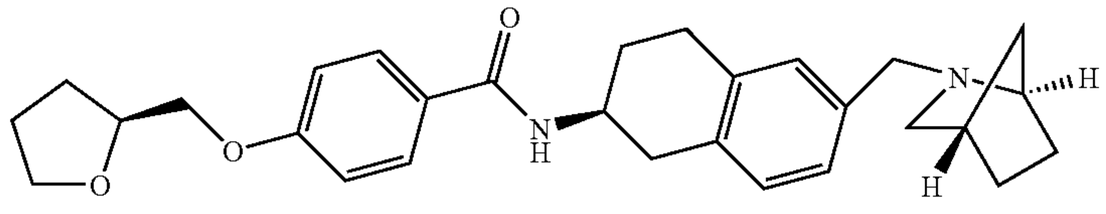
Ex. No.	Structure	Molecular-weight	ESI-MS $[M + H]^+$
3-141		450.62	451
3-142		436.59	437
3-143		461.60	462
3-144		490.64	491
3-145		474.64	475
3-146		503.64	504
3-147		460.61	461
3-148		460.61	461

TABLE 1-continued

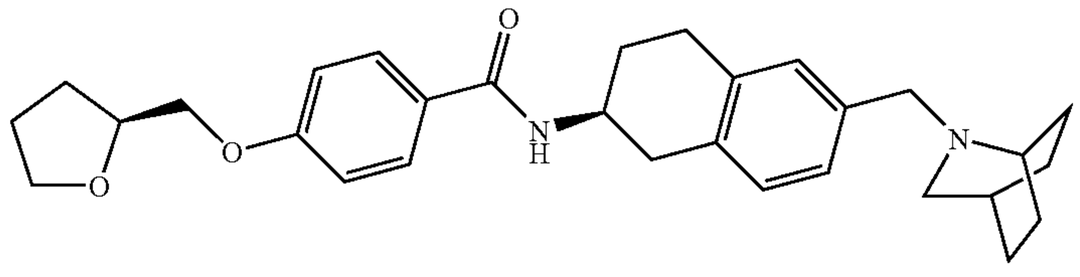
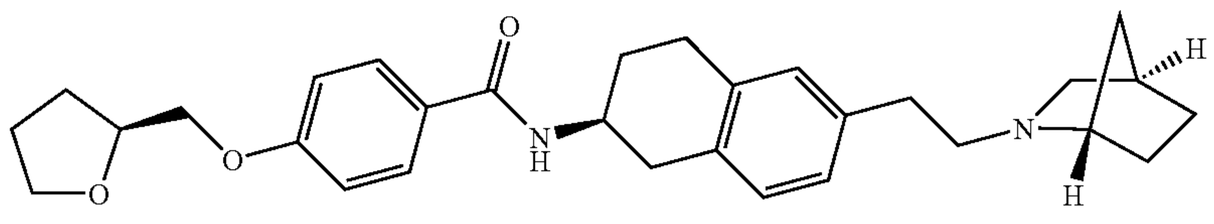
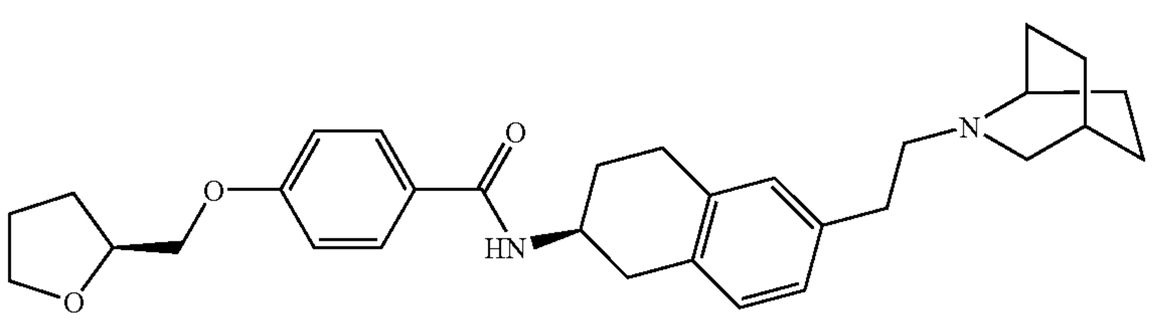
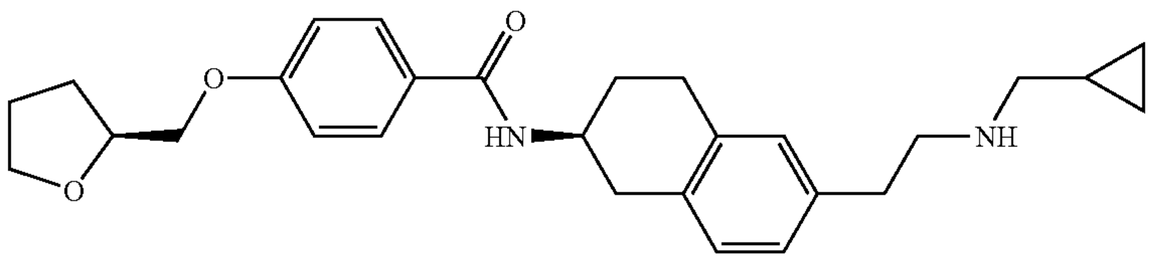
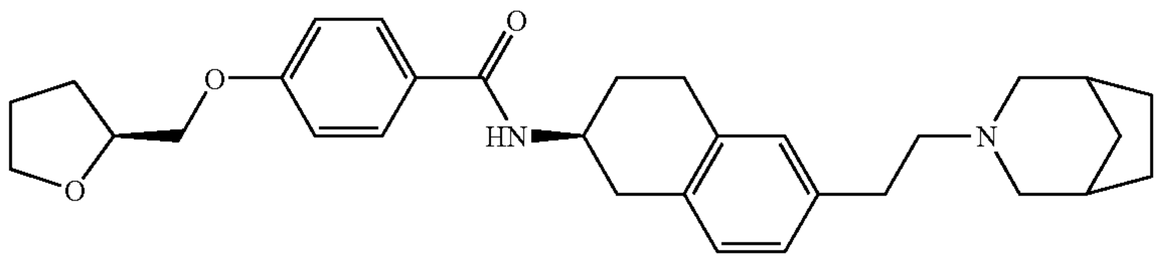
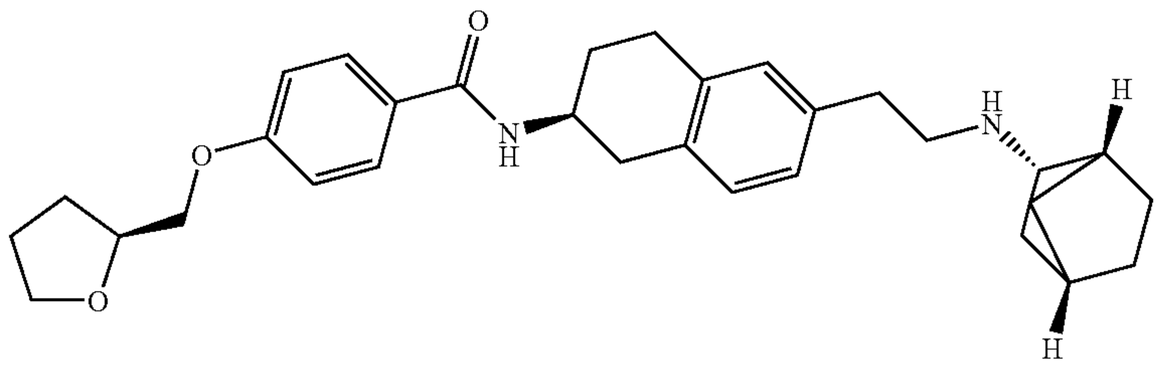
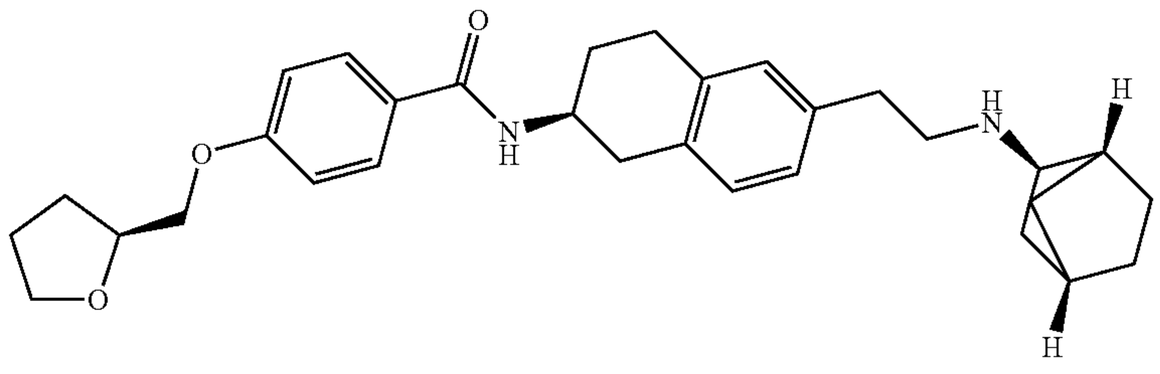
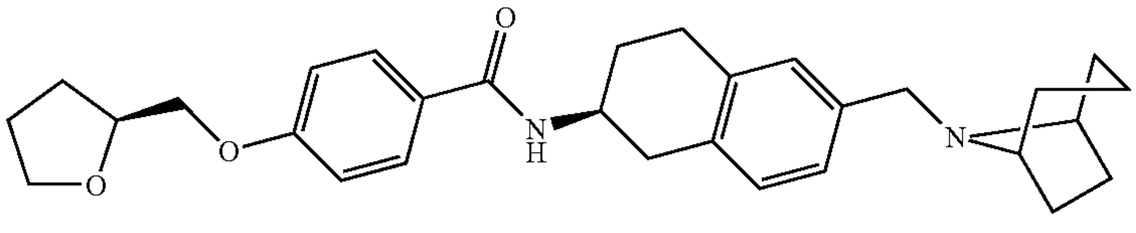
Ex. No.	Structure	Molecular-weight	ESI-MS $[M + H]^+$
3-149		474.64	475
3-150		474.64	475
3-151		488.67	489
3-152		448.60	449
3-153		488.67	489
3-154		488.67	489
3-155		488.67	489
3-156		474.64	475

TABLE 1-continued

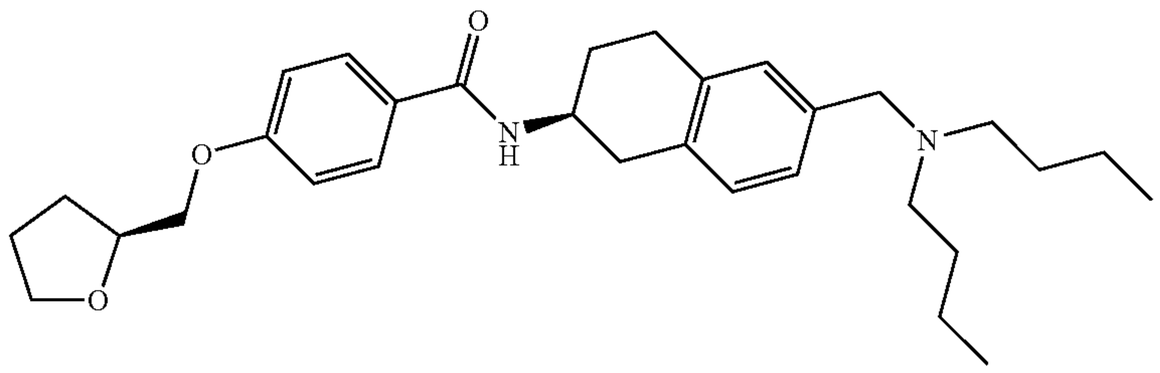
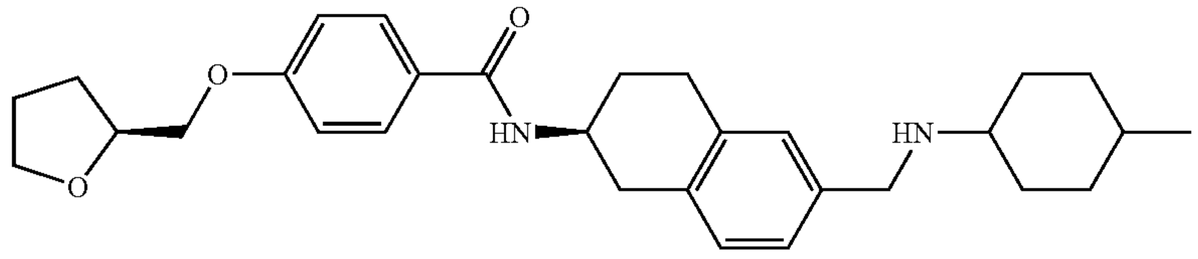
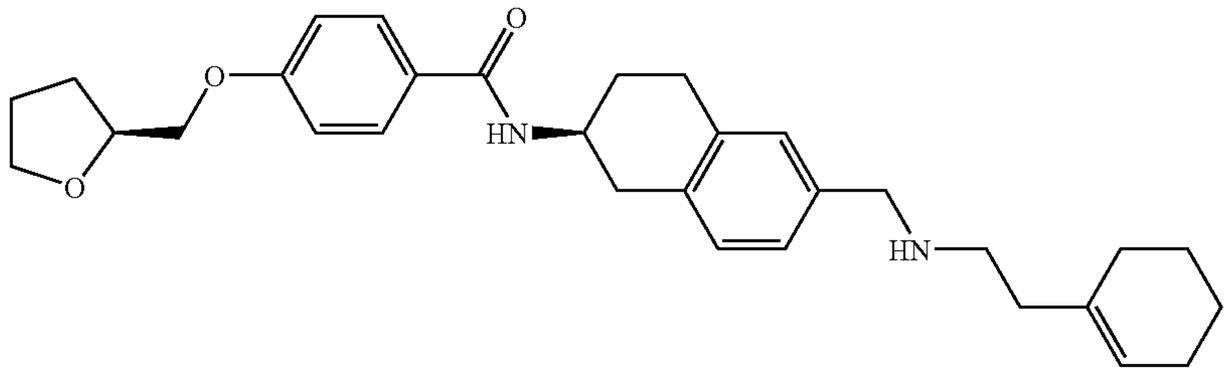
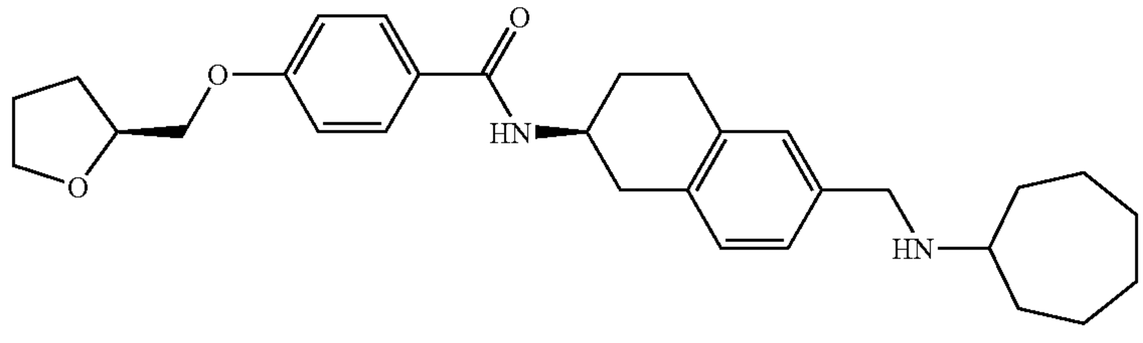
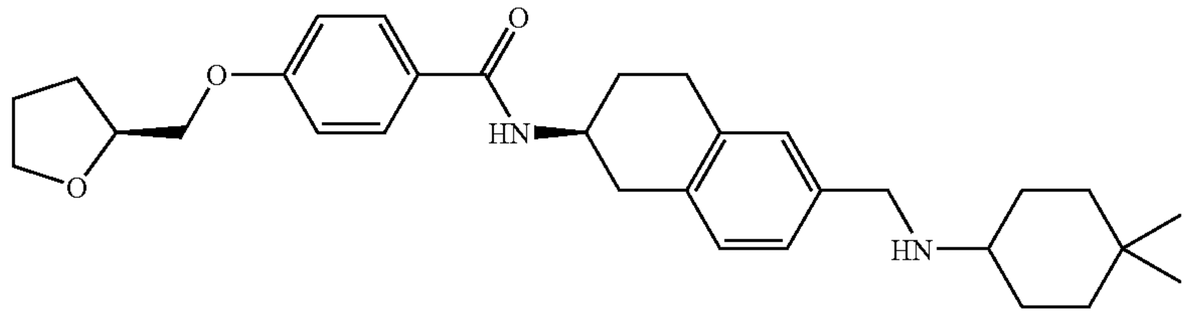
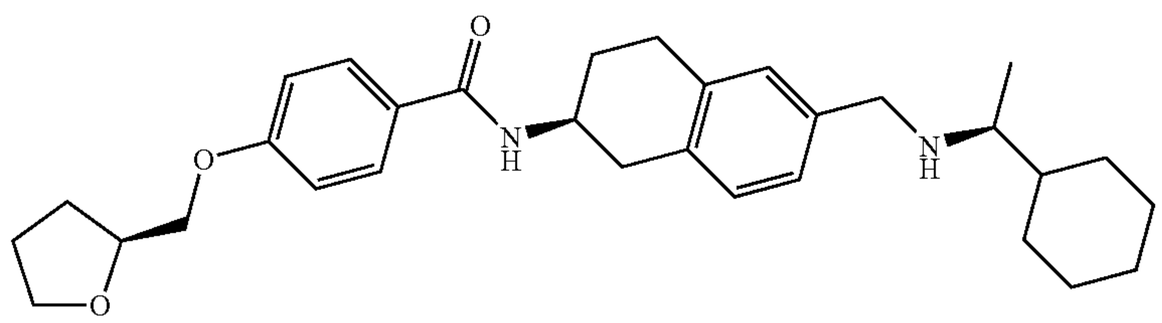
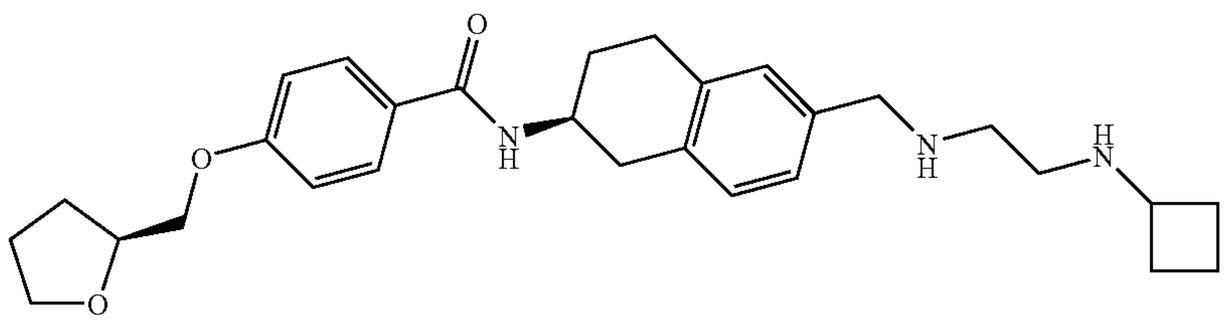
Ex. No.	Structure	Molecular-weight	ESI-MS $[M + H]^+$
3-157		492.70	493
3-158		476.66	477
3-159		488.67	489
3-160		476.66	477
3-161		490.68	491
3-162		490.68	491
3-163		477.65	478

TABLE 1-continued

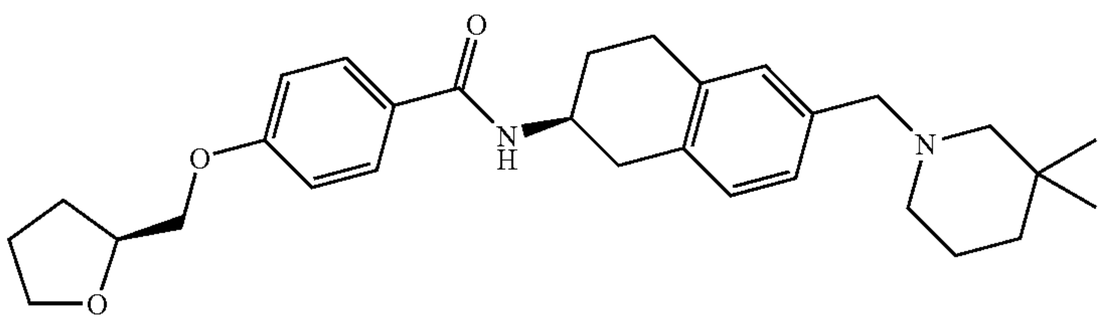
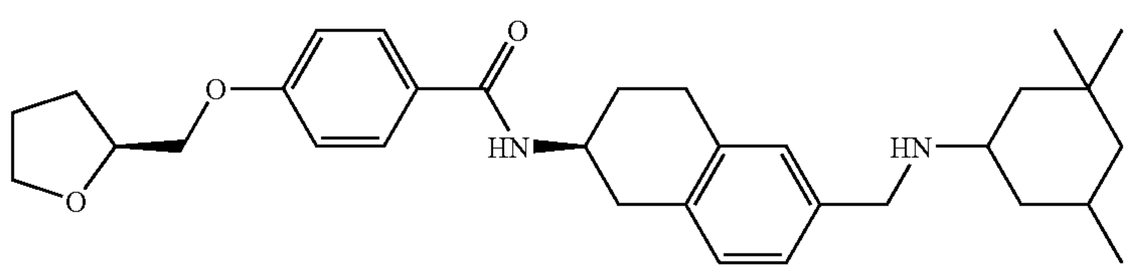
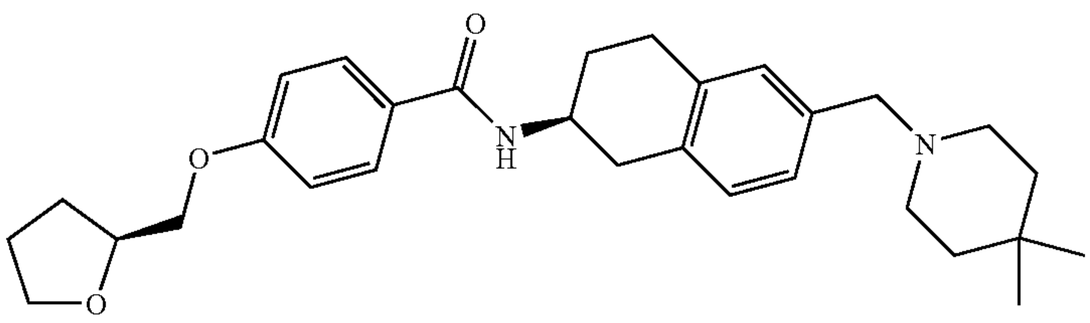
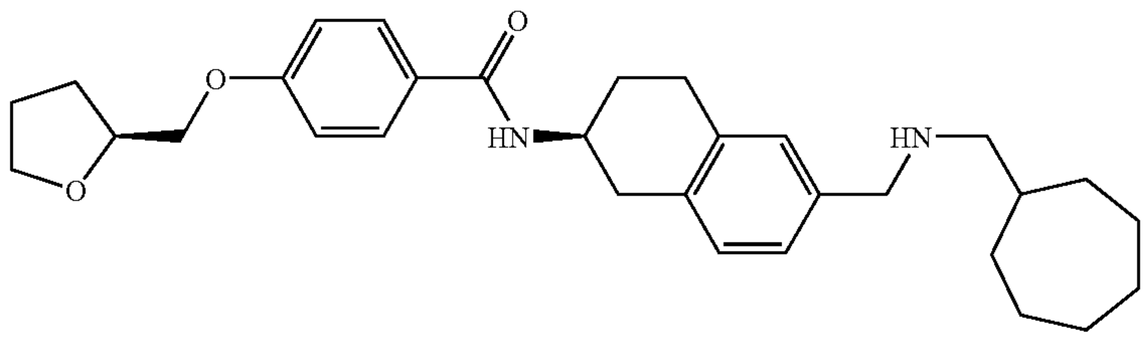
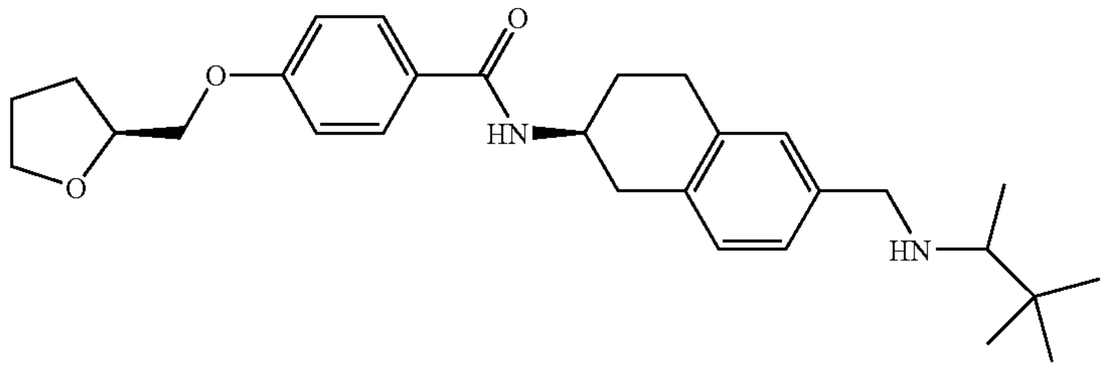
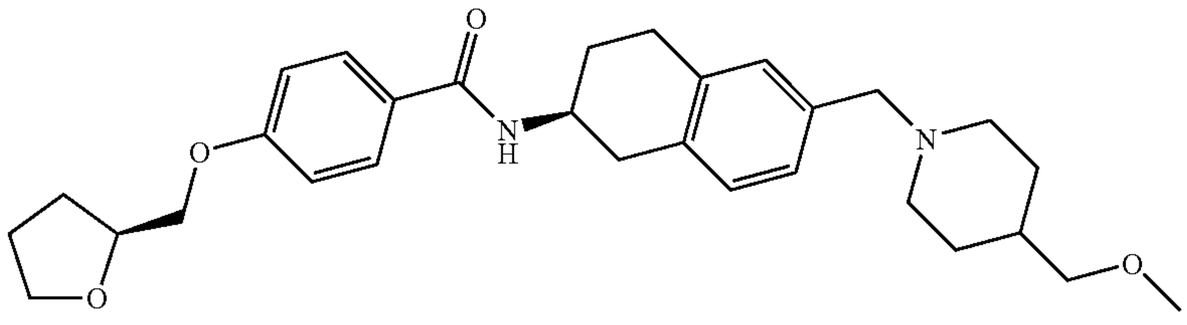
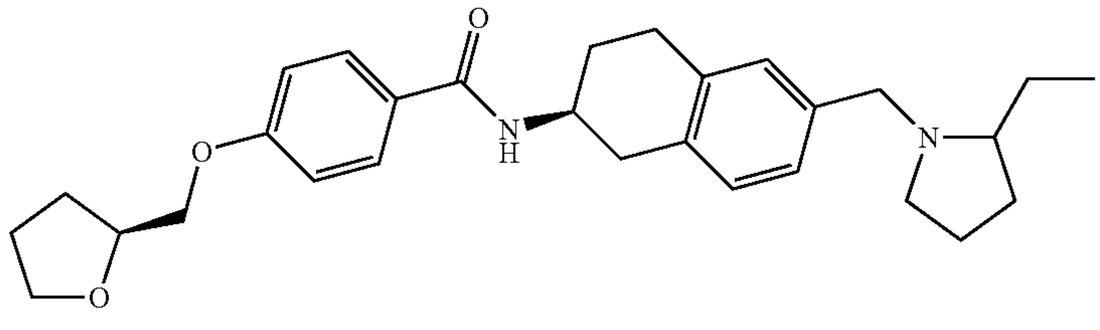
Ex. No.	Structure	Molecular-weight	ESI-MS $[M + H]^+$
3-164		476.66	477
3-165		504.71	505
3-166		476.66	477
3-167		490.68	491
3-168		464.65	465
3-169		492.66	493
3-170		462.63	463

TABLE 1-continued

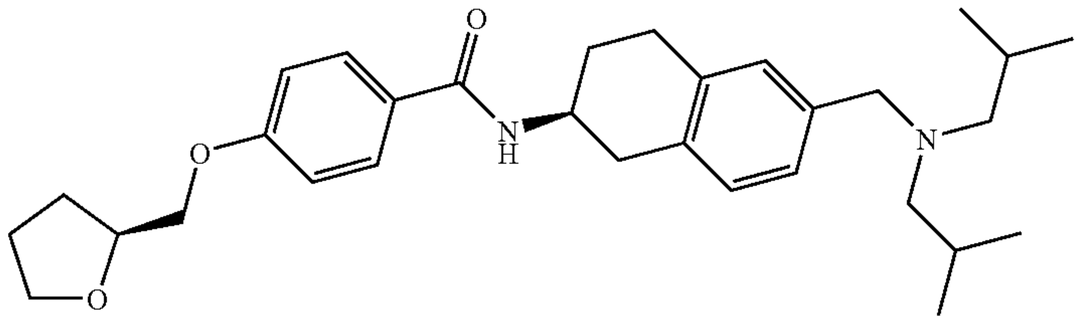
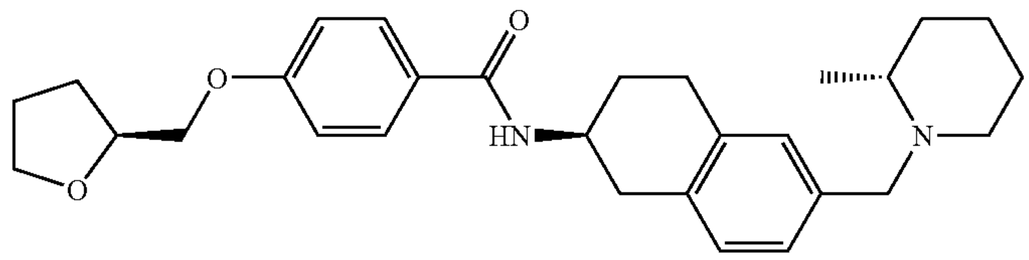
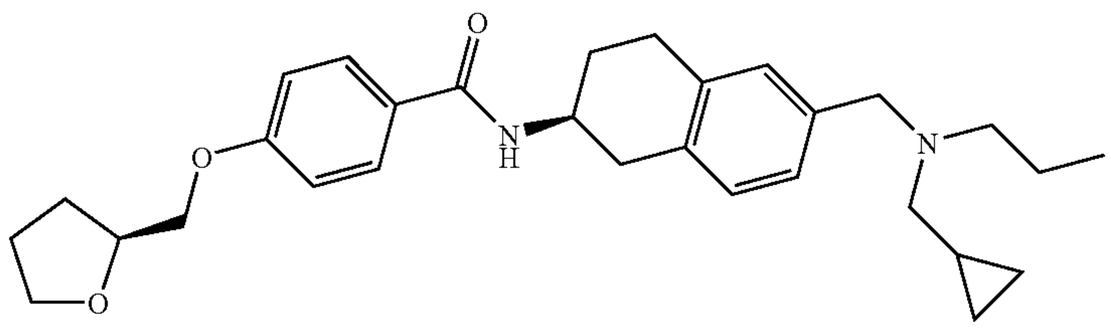
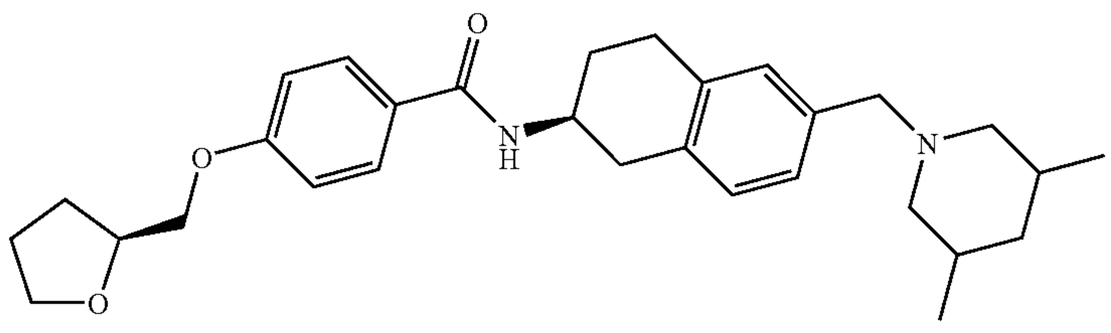
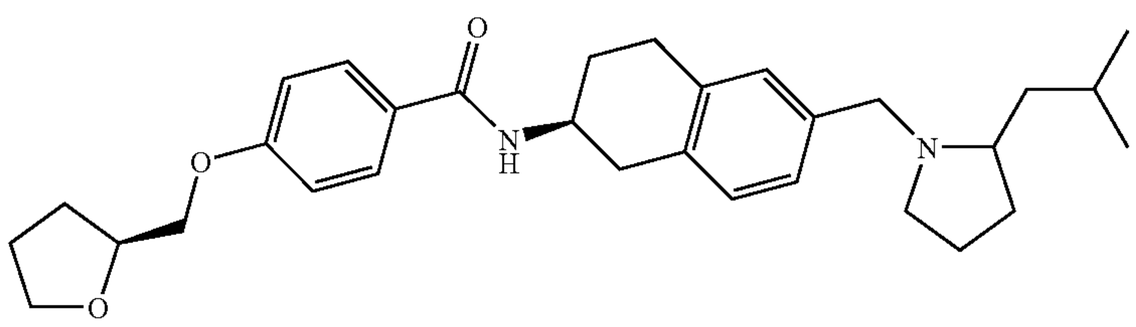
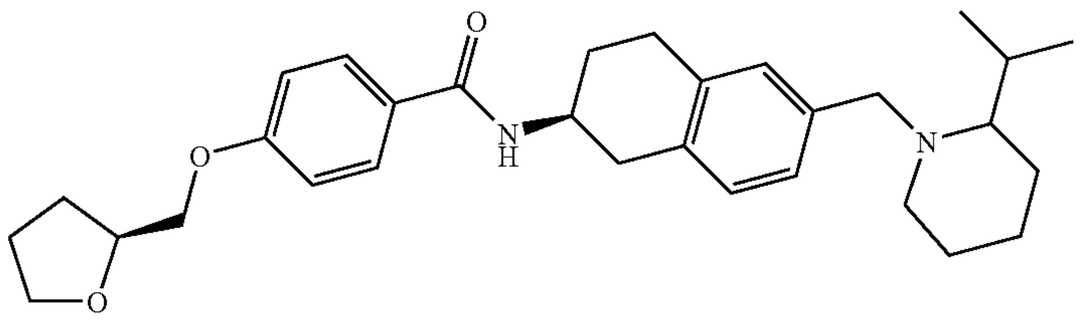
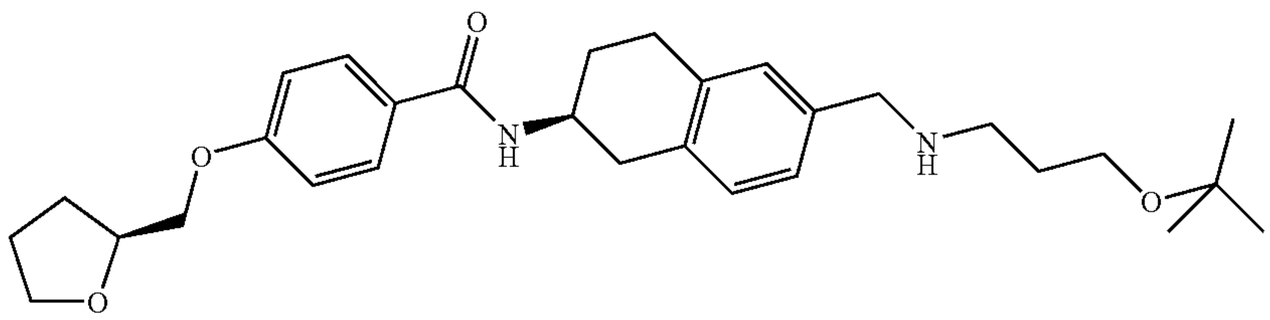
Ex. No.	Structure	Molecular-weight	ESI-MS $[M + H]^+$
3-171		492.70	493
3-172		462.63	463
3-173		476.66	477
3-174		476.66	477
3-175		490.68	491
3-176		490.68	491
3-177		494.67	495

TABLE 1-continued

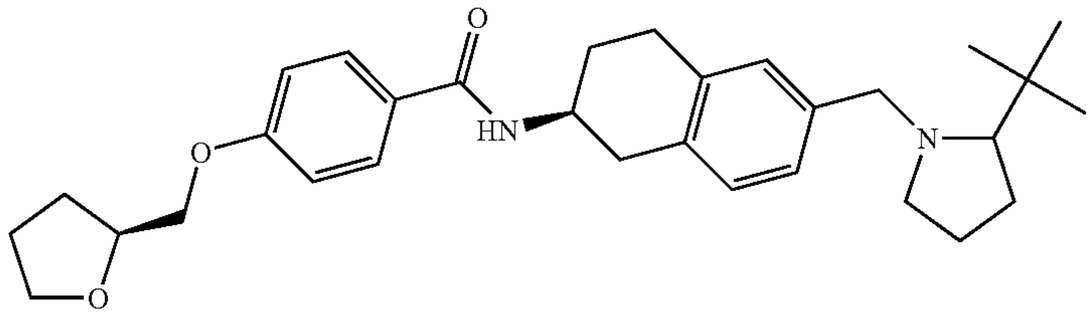
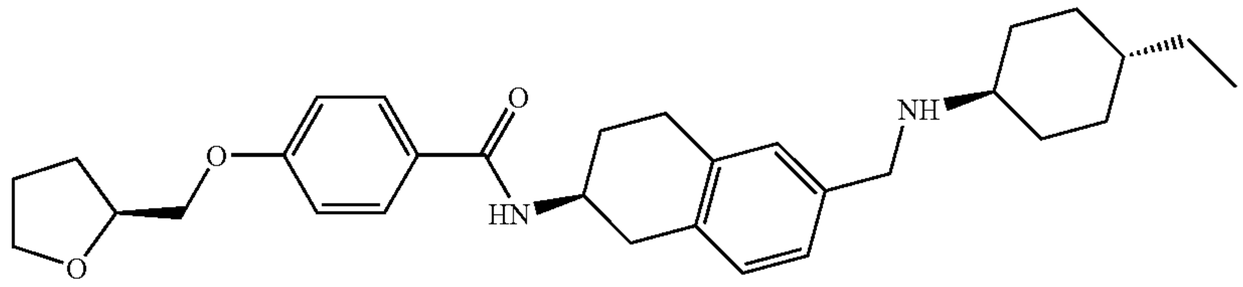
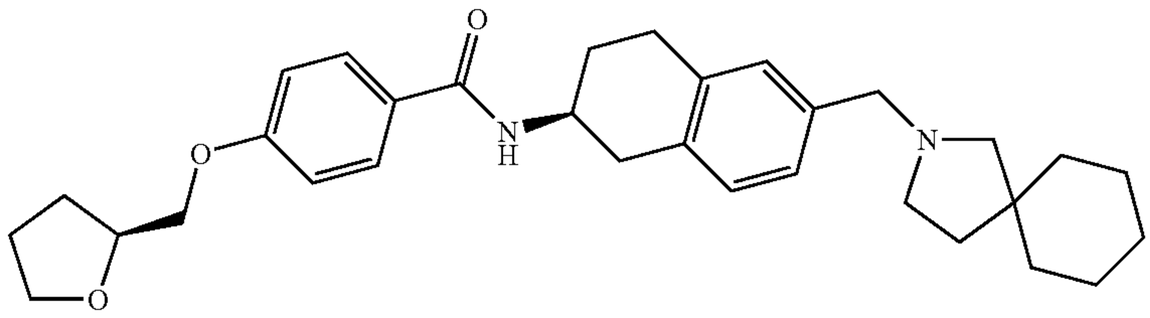
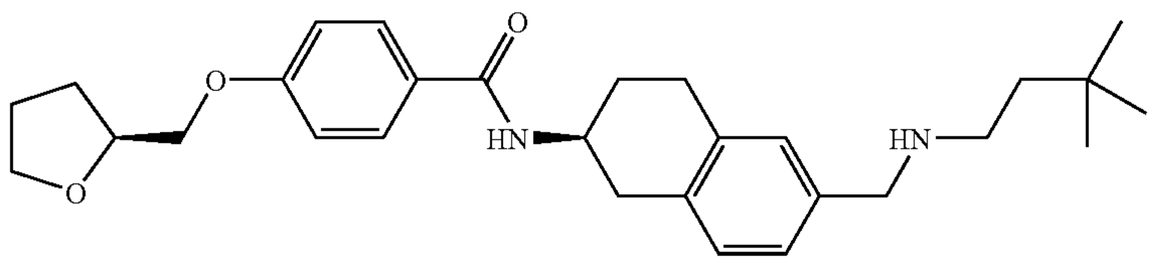
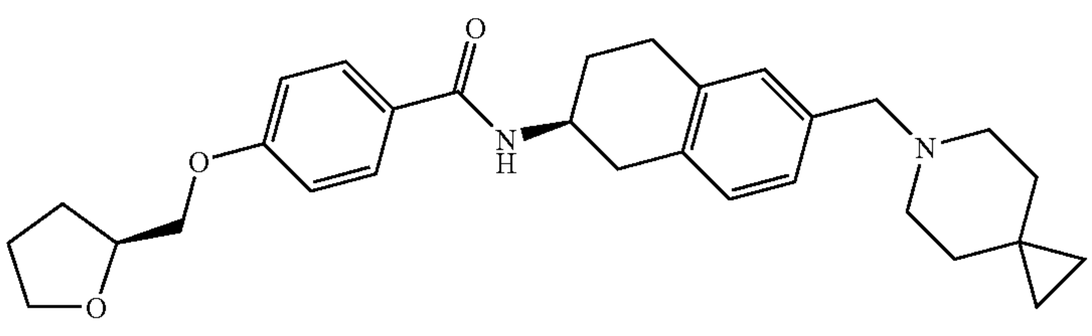
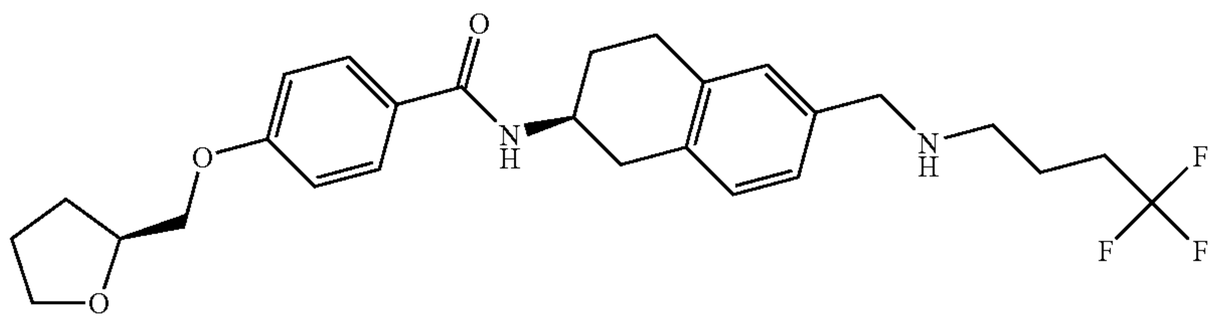
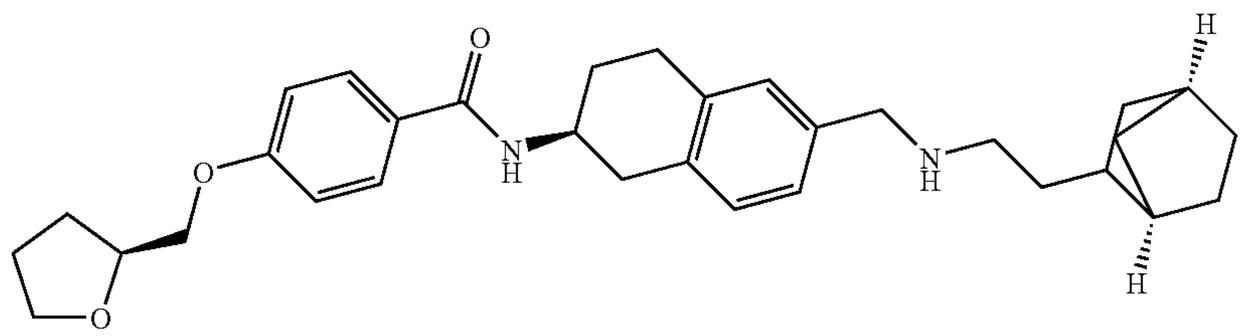
Ex. No.	Structure	Molecular-weight	ESI-MS $[M + H]^+$
3-178		490.68	491
3-179		490.68	491
3-180		502.70	503
3-181		464.65	465
3-182		474.64	475
3-183		490.56	491
3-184		502.70	503

TABLE 1-continued

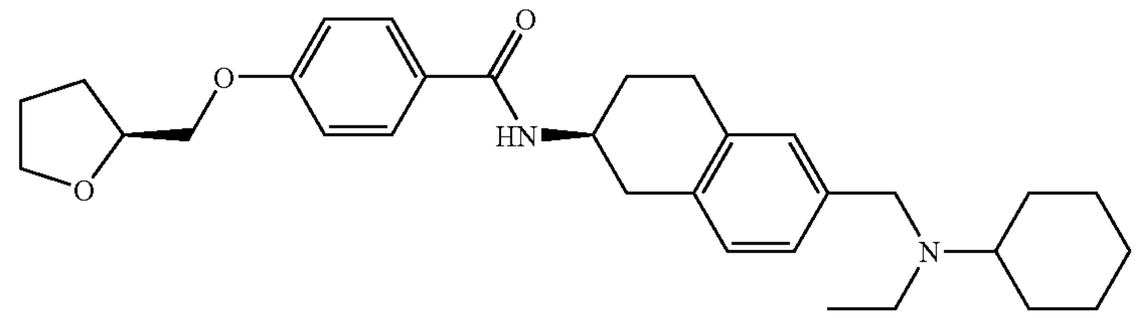
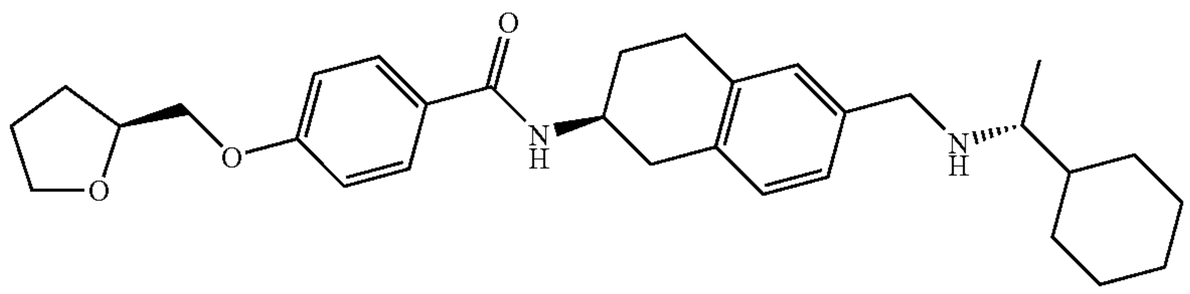
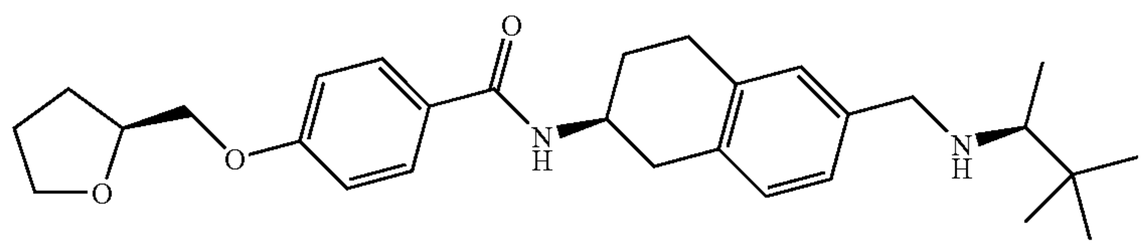
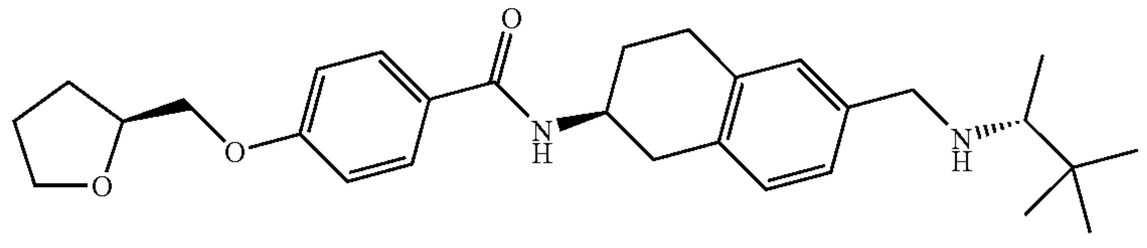
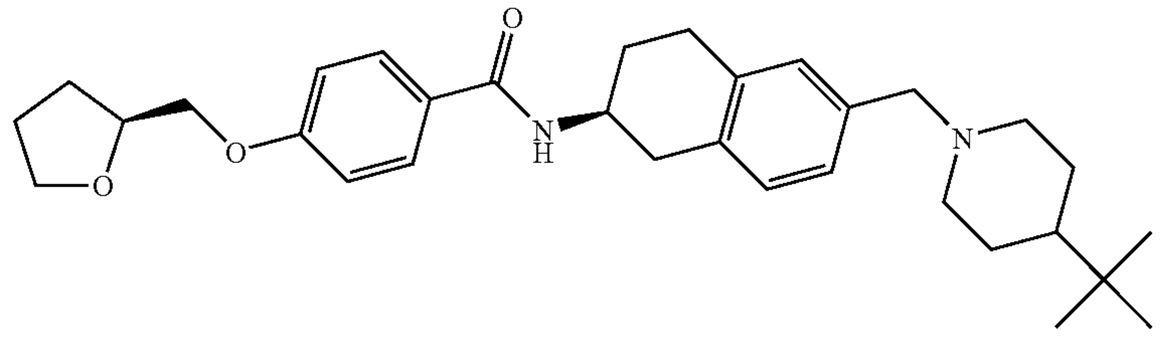
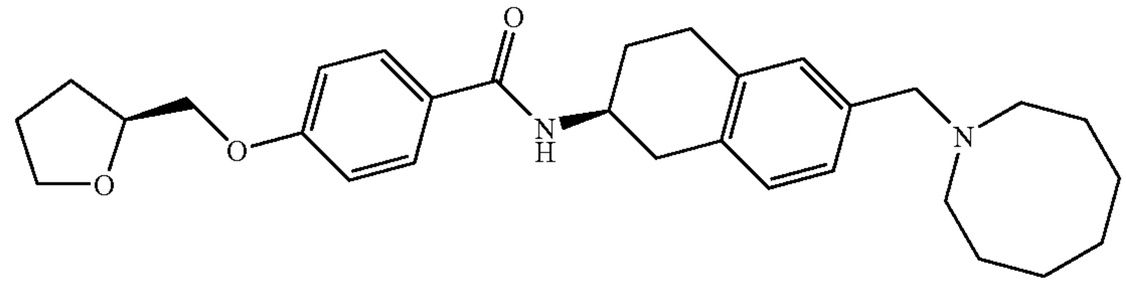
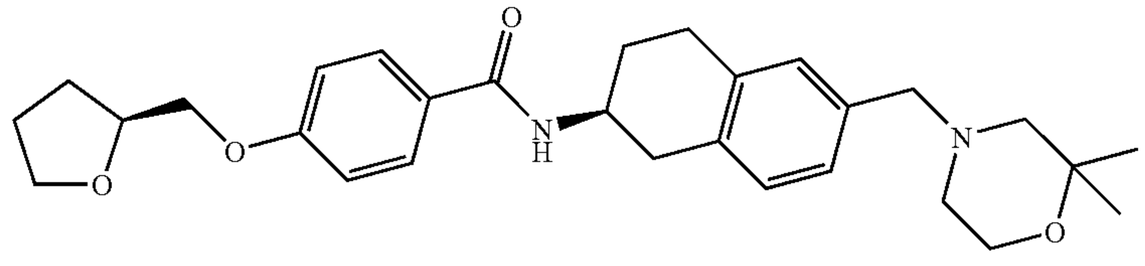
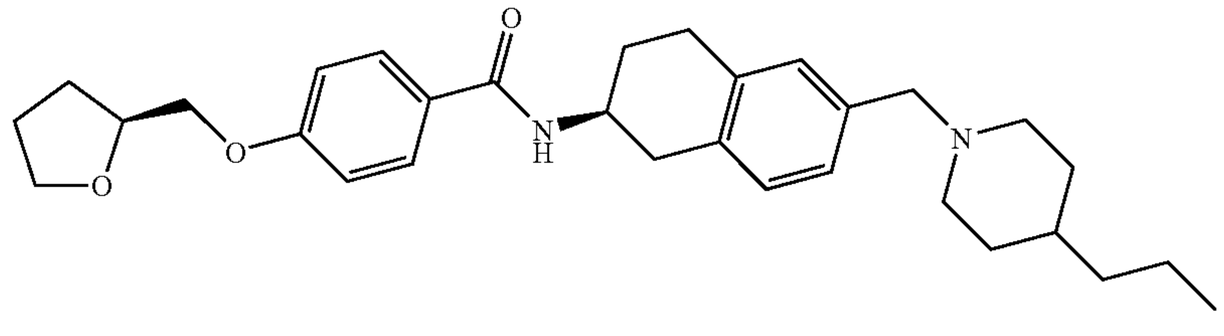
Ex. No.	Structure	Molecular-weight	ESI-MS [M + H]+
3-185		490.68	491
3-186		490.68	491
3-187		464.65	465
3-188		464.65	465
3-189		504.71	505
3-190		476.66	477
3-191		478.63	479
3-192		490.68	491

TABLE 1-continued

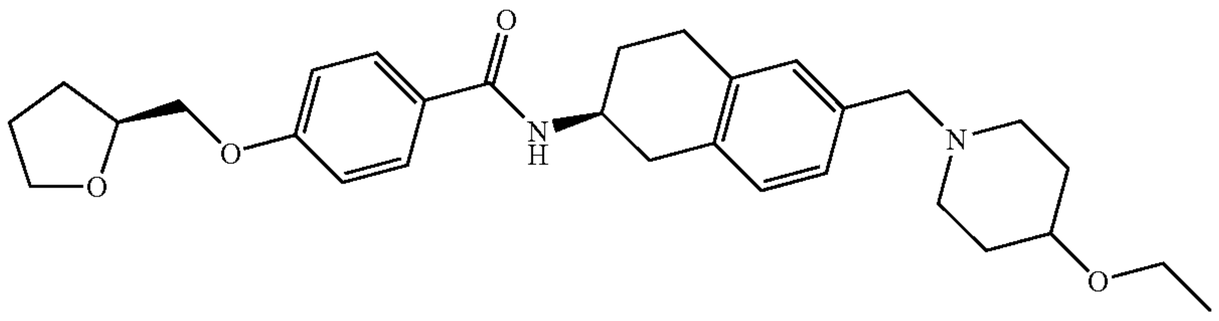
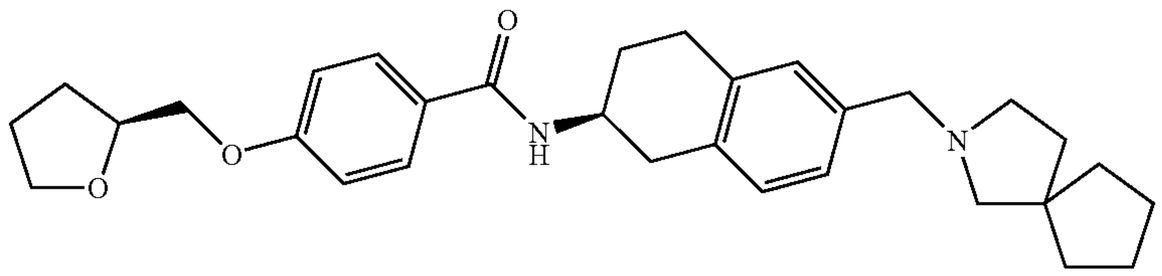
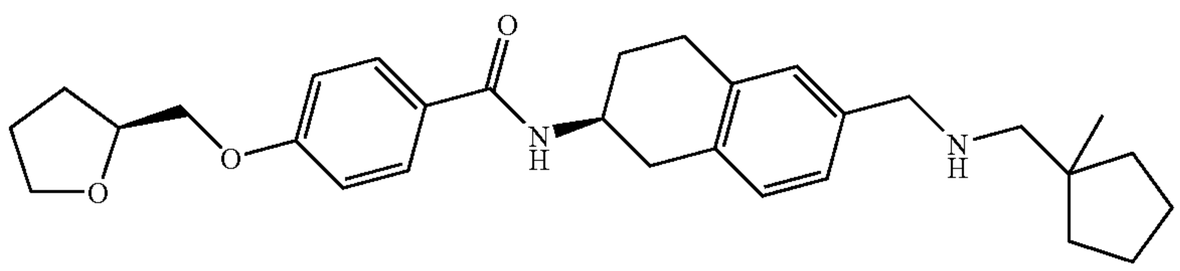
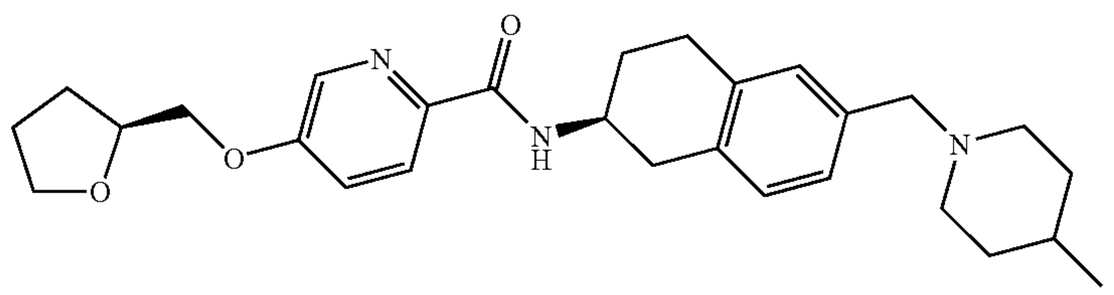
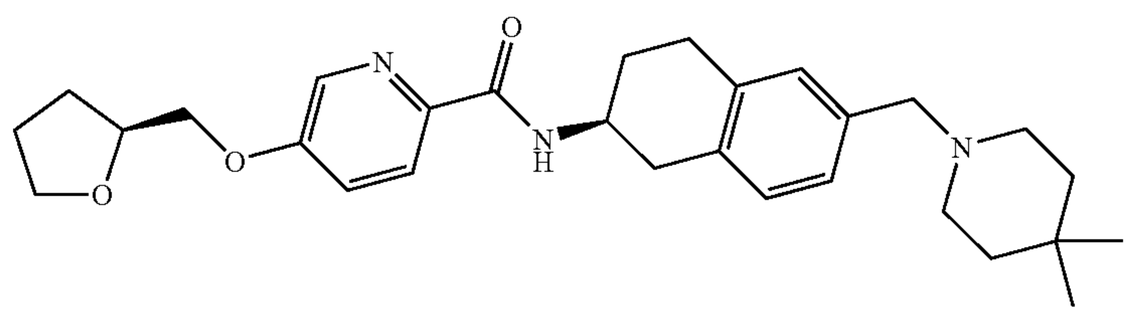
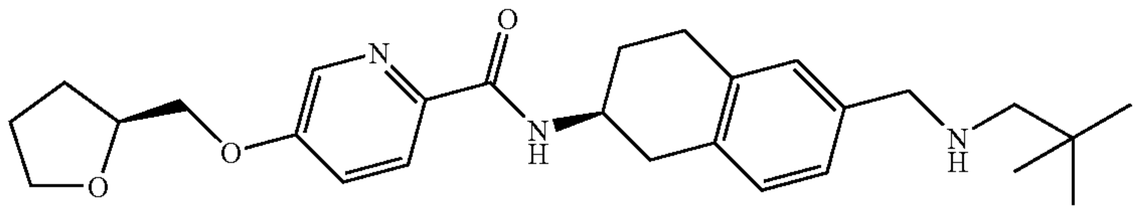
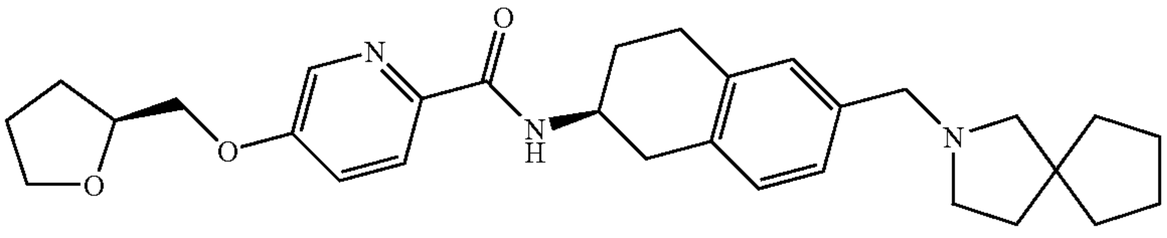
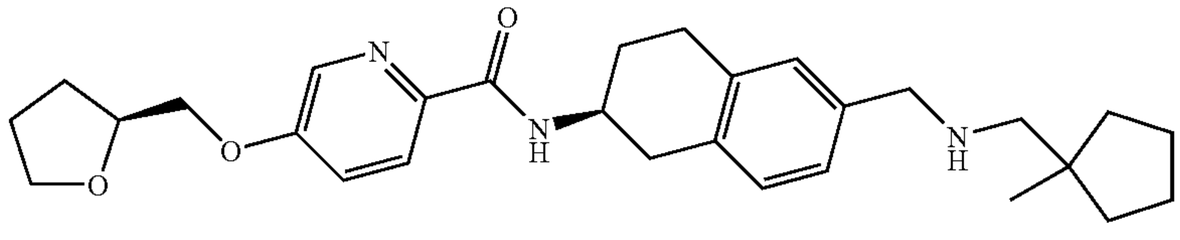
Ex. No.	Structure	Molecular-weight	ESI-MS $[M + H]^+$
3-193		492.66	493
3-194		488.67	489
3-195		476.66	477
3-196		463.63	464
3-197		477.65	478
3-198		451.61	452
3-199		489.66	490
3-200		477.65	478

TABLE 1-continued

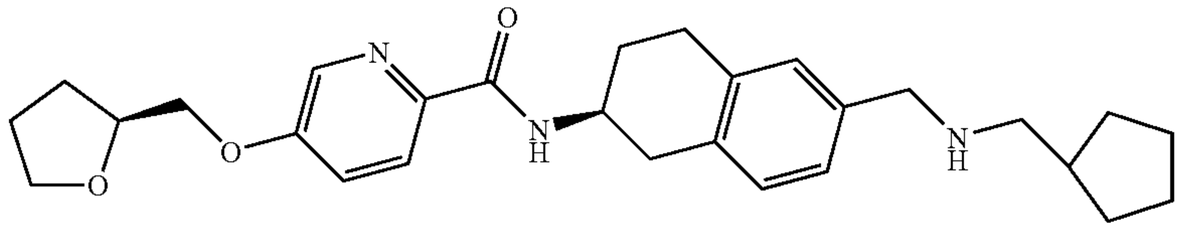
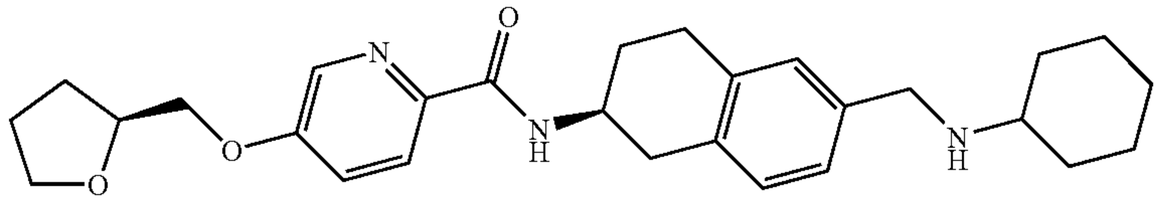
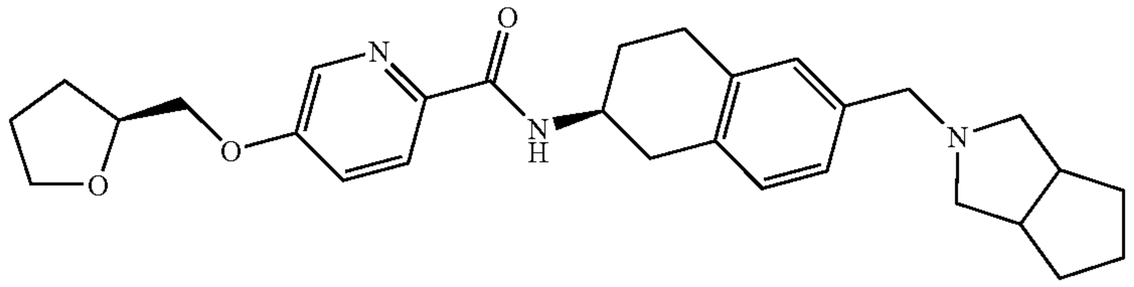
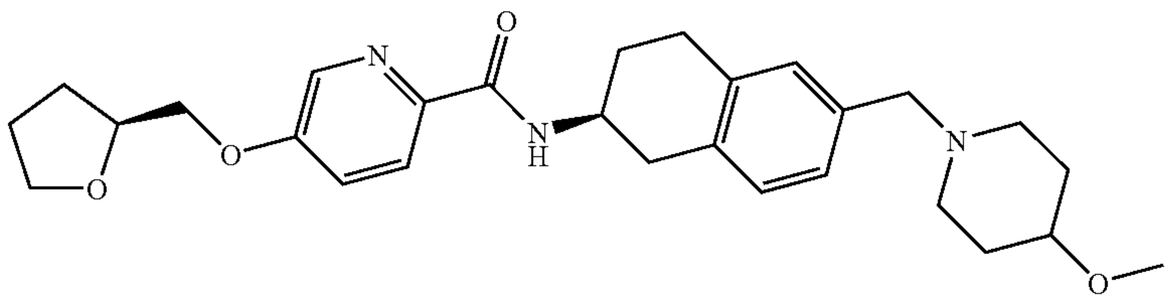
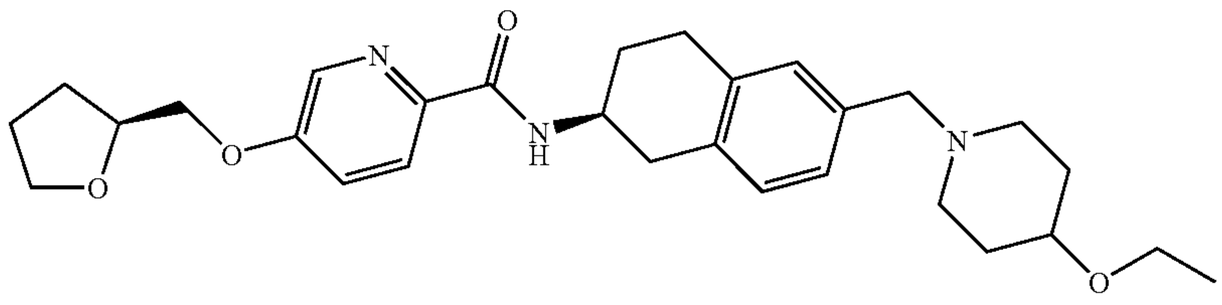
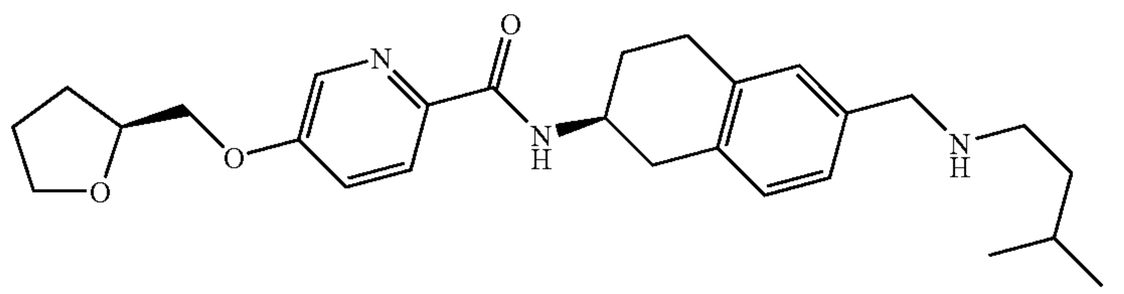
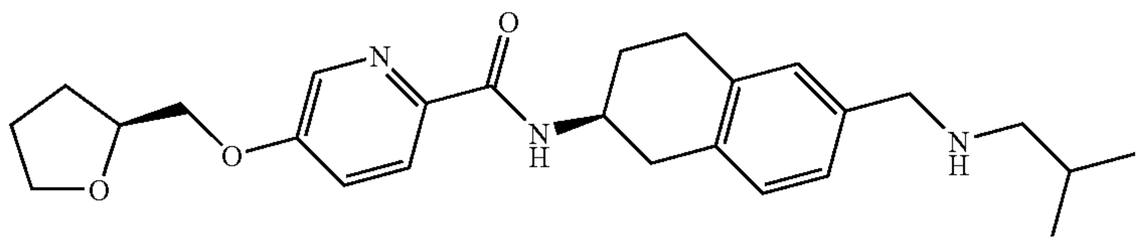
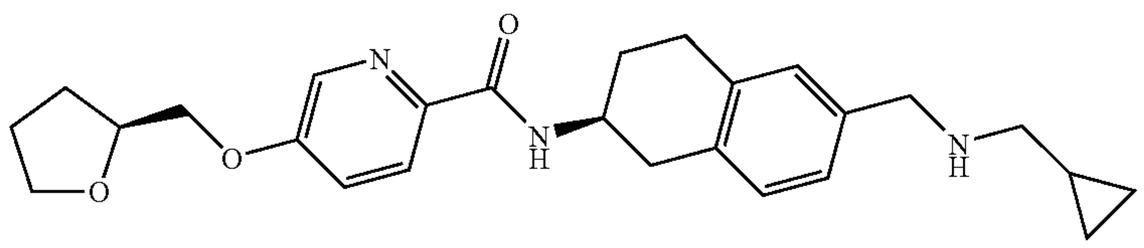
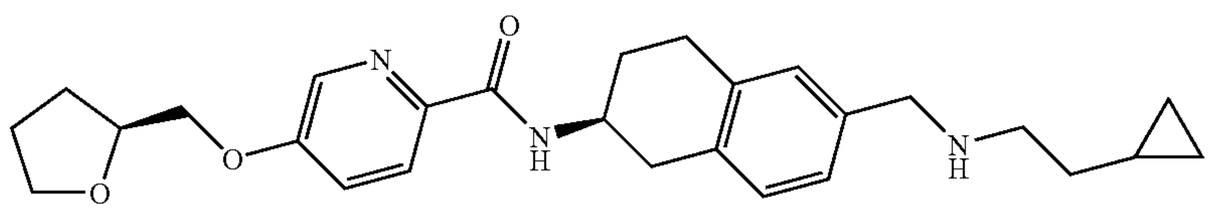
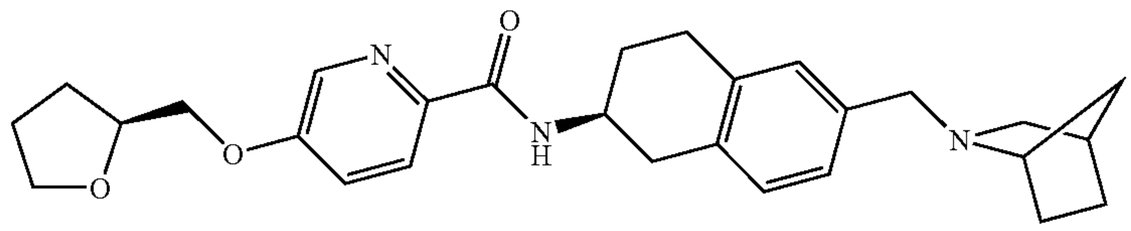
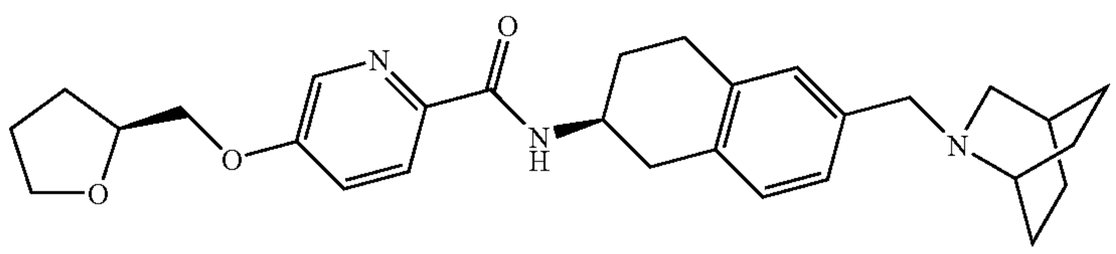
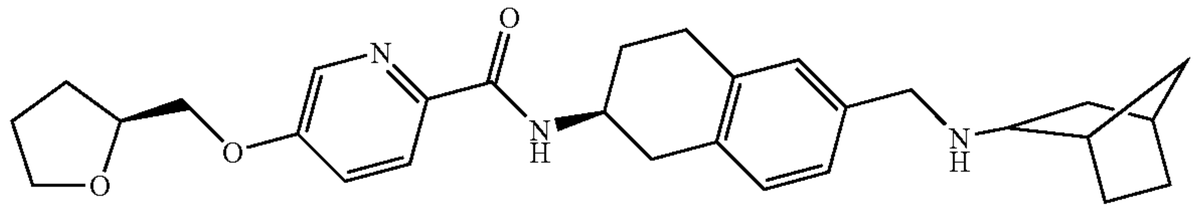
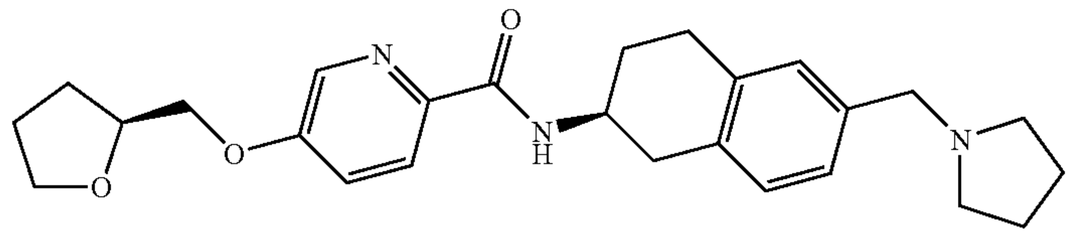
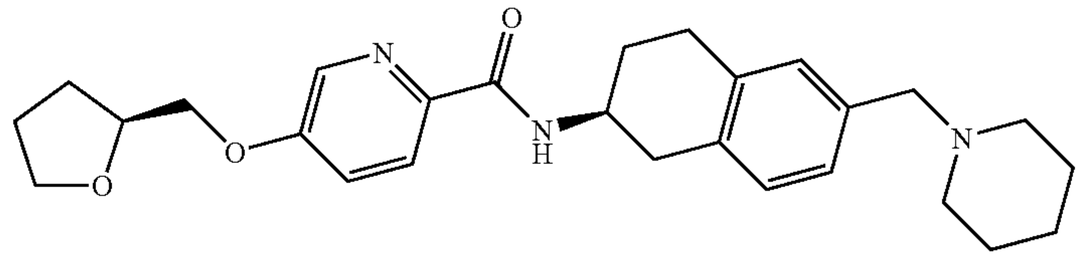
Ex. No.	Structure	Molecular-weight	ESI-MS $[M + H]^+$
3-201		463.63	464
3-202		463.63	464
3-203		475.64	476
3-204		479.62	480
3-205		493.65	494
3-206		451.61	452
3-207		437.59	438
3-208		435.57	436
3-209		449.60	450

TABLE 1-continued

Ex. No.	Structure	Molecular-weight	ESI-MS $[M + H]^+$
3-210		461.61	462
3-211		475.64	476
3-212		475.64	476
3-213		435.57	436
3-214		449.60	450

Preparation of Starting Materials Required (Table 1)

N-((S)-6-Acetyl-1,2,3,4-tetrahydronaphthalen-2-yl)-4-[(S)-1-(tetrahydrofuran-2-yl)methoxy]benzamide

A mixture of N-((S)-6-bromo-1,2,3,4-tetrahydronaphthalen-2-yl)-4-[(S)-1-(tetrahydrofuran-2-yl)methoxy]benzamide (1.0 g) and THF (10 ml) was cooled to −78° C. (dry ice bath), and a solution of methyllithium (2.0 ml; 1.6 M in diethyl ether) was added dropwise. One minute after the addition had ended, a solution of butyllithium (1.4 ml; 2.5 M in toluene) was added dropwise. One minute after the addition had ended, N-methoxy-N-methylacetamide (0.24 g) was added. After warming to room temperature, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic phases were dried over magnesium sulfate and concentrated. The residue was chromatographed on silica gel (eluent: 1:1 heptane/ethyl acetate). The product was thus obtained with the molecular weight of 393.49 (C24H27NO4); MS (ESI): 394 (M+H+).

N-[(S)-6-(2-Oxoethyl)-1,2,3,4-tetrahydronaphthalen-2-yl]-4-[(S)-1-(tetrahydrofuran-2-yl)methoxy]benzamide

A mixture of N-((S)-6-allyl-1,2,3,4-tetrahydronaphthalen-2-yl)-4-[(S)-1-(tetrahydrofuran-2-yl)methoxy]benzamide (0.50 g), 2-propanol (50 ml) and water (50 ml) was admixed with sodium periodate (0.60 g) and osmium tetroxide (1.3 mg). After stirring vigorously for 14 hours, the reaction mixture was extracted with ethyl acetate. The organic phase was washed with sodium chloride solution, dried over sodium sulfate and concentrated. The product was thus obtained with the molecular weight of 393.49 (C24H27NO4); MS (ESI): 394 (M+H+).

N-((S)-6-Allyl-1,2,3,4-tetrahydronaphthalen-2-yl)-4-[(S)-1-(tetrahydrofuran-2-yl)methoxy]benzamide

A mixture of N-((S)-6-bromo-1,2,3,4-tetrahydronaphthalen-2-yl)-4-[(S)-1-(tetrahydrofuran-2-yl)methoxy]benzamide (1.00 g), toluene (10 ml), $Pd(PPh_3)_4$ (26.7 mg) and allyltributyltin (2.46 g) was boiled at reflux for 5 hours. The cooled reaction mixture was diluted with ethyl acetate and washed with water. The organic phase was washed with sodium chloride solution, dried over sodium sulfate and concentrated. The residue was purified by chromatography on silica gel. The product was thus obtained with the molecular weight of 391.51 (C25H29NO3); MS (ESI): 392 (M+H+).

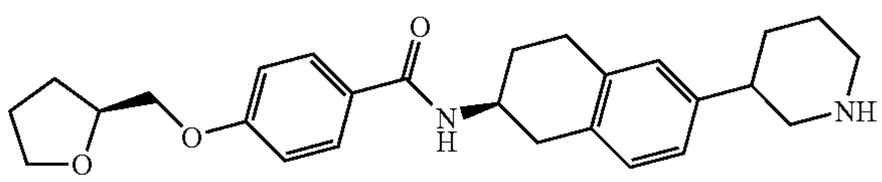
N-((S)-6-formyl-1,2,3,4-tetrahydronaphthalen-2-yl)-5-[(S)-1-(tetrahydrofuran-2-yl)methoxy]pyridine-2-carboxamide

According to method A, (S)-6-bromo-1,2,3,4-tetrahydronaphthalen-2-ylamine was reacted with 5-hydroxypyri-

dine-2-carboxylic acid. The amide obtained was alkylated by method F with (S)-1-(tetrahydrofuran-2-yl)methyl methanesulfonate and converted to the desired aldehyde by method I. The product was thus obtained with the molecular weight of 380.45 ($C_{22}H_{24}N_2O_4$); MS (ESI): 381 (M+H+).

Example 4

N-((S)-6-Piperidin-3-yl-1,2,3,4-tetrahydronaphthalen-2-yl)-4-[(S)-1-(tetrahydrofuran-2-yl)methoxy]benzamide



Method J-1

A mixture of N-((S)-6-pyridin-3-yl-1,2,3,4-tetrahydronaphthalen-2-yl)-4-[(S)-1-(tetrahydrofuran-2-yl)methoxy]benzamide (0.60 g), glacial acetic acid (30 ml) and platinum(IV) oxide (0.10 g) was stirred vigorously under a hydrogen atmosphere (balloon) for 12 hours. The catalyst was filtered off with suction and the filtrate was concentrated. The product was thus obtained with the molecular weight of 434.58 ($C_{27}H_{34}N_2O_3$); MS (ESI): 435 (M+H+).

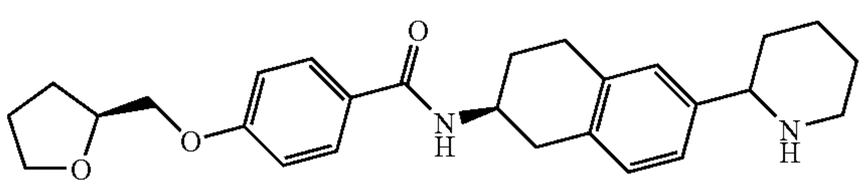
Preparative separation on a chiral phase (Chiralpak AD-H) afforded the pure diastereomers (N-((S)-(R)-6-piperidin-3-yl-1,2,3,4-tetrahydronaphthalen-2-yl)-4-[(S)-1-(tetrahydrofuran-2-yl)methoxy]benzamide and N-((S)-(S)-6-piperidin-3-yl-1,2,3,4-tetrahydronaphthalen-2-yl)-4-[(S)-1-(tetrahydrofuran-2-yl)methoxy]benzamide).

N-((S)-6-Pyridin-3-yl-1,2,3,4-tetrahydronaphthalen-2-yl)-4-[(S)-1-(tetrahydrofuran-2-yl)methoxy]benzamide

A mixture of N-((S)-6-bromo-1,2,3,4-tetrahydronaphthalen-2-yl)-4-[(S)-1-(tetrahydrofuran-2-yl)methoxy]benzamide (1.00 g), toluene (10 ml) and $Pd(PPh_3)_4$ (2.69 g) was admixed with 3-pyridylboronic acid (0.28 g), ethanol (3 ml) and cesium carbonate solution (1.2 ml; 2 M in water). The mixture was boiled at reflux for 7 hours. The cooled reaction mixture was diluted with ethyl acetate and washed with water. The organic phase was washed with sodium chloride solution, dried over sodium sulfate and concentrated. The residue was purified by chromatography on silica gel. The product was thus obtained with the molecular weight of 428.54 ($C_{27}H_{28}N_2O_3$); MS (ESI): 429 (M+H+).

Example 5

N-((S)-6-Piperidin-2-yl-1,2,3,4-tetrahydronaphthalen-2-yl)-4-[(S)-1-(tetrahydrofuran-2-yl)methoxy]benzamide



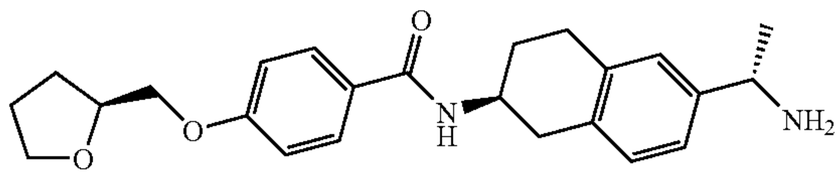
According to method J-1, N-[(S)-6-(1-oxypyridin-2-yl)-1,2,3,4-tetrahydronaphthalen-2-yl]-4-[(S)-1-(tetrahydrofuran-2-yl)methoxy]-benzamide was hydrogenated. The product was thus obtained with the molecular weight of 434.58 ($C_{27}H_{34}N_2O_3$); MS (ESI): 435 (M+H+).

N-[(S)-6-(1-Oxypyridin-2-yl)-1,2,3,4-tetrahydronaphthalen-2-yl]-4-[(S)-1-(tetrahydrofuran-2-yl)methoxy]benzamide

A mixture of pyridine N-oxide (0.88 g), potassium carbonate (0.64 g), tri-tert-butylphosphine (0.101 g; HBF_4 adduct) and palladium(II) acetate (26 mg) was admixed with a solution of N-((S)-6-bromo-1,2,3,4-tetrahydronaphthalen-2-yl)-4-[(S)-1-(tetrahydrofuran-2-yl)methoxy]benzamide (1.00 g) in toluene (8 ml). The mixture was boiled at reflux for 5 hours. The cooled reaction mixture was diluted with ethyl acetate and washed with water. The organic phase was washed with sodium chloride solution, dried over sodium sulfate and concentrated. The residue was purified by chromatography on silica gel (eluent: 15:1 dichloromethane/methanol). The product was thus obtained with the molecular weight of 444.54 ($C_{27}H_{28}N_2O_4$); MS (ESI): 445 (M+H+).

Example 6

N-[(S)-6-((S)-1-Aminoethyl)-1,2,3,4-tetrahydronaphthalen-2-yl]-4-[(S)-1-(tetrahydrofuran-2-yl)methoxy]benzamide



Method K

A mixture of N-{(S)-6-[(S)-1-((R)-2-methylpropane-2-sulfinylamino)ethyl]-1,2,3,4-tetrahydronaphthalen-2-yl}-4-[(S)-1-(tetrahydrofuran-2-yl)methoxy]-benzamide (0.12 g) and methanol (2 ml) was admixed with hydrogen chloride (2 ml; 5 M in 2-propanol). After 30 minutes, the reaction mixture was concentrated. The product was thus obtained with the molecular weight of 394.52 ($C_{24}H_{30}N_2O_3$); MS (ESI): 395 (M+H+).

In an analogous manner, it is possible to prepare N-[(S)-6-((R)-1-aminoethyl)-1,2,3,4-tetrahydronaphthalen-2-yl]-4-[(S)-1-(tetrahydrofuran-2-yl)methoxy]-benzamide.

N-{(S)-6-[(S)-1-((R)-2-Methylpropane-2-sulfinylamino)ethyl]-1,2,3,4-tetrahydro-naphthalen-2-yl}-4-[(S)-1-(tetrahydrofuran-2-yl)methoxy]benzamide

Method L

A suspension, cooled to −45° C., of N-((S)-6-{[(E)-(R)-2-methylpropane-2-sulfinylimino]methyl}-1,2,3,4-tetrahydronaphthalen-2-yl)-4-[(S)-1-(tetrahydrofuran-2-yl)methoxy]benzamide (0.34 g), diethyl ether (15 ml) and dichloromethane (15 ml) was admixed with methylmagnesium bromide (1.1 ml; 1.4 M in toluene). After warming to room temperature, the mixture was stirred for another 5 hours. The reaction mixture was hydrolyzed cautiously with water and extracted with ethyl acetate. The organic phase was washed with sodium chloride solution, dried over sodium sulfate and concentrated. The residue was purified by chro-

matography on silica gel (eluent: ethyl acetate). The product was thus obtained with the molecular weight of 498.69 ($C_{28}H_{38}N_2O_4S$); MS (ESI): 499 (M+H+).

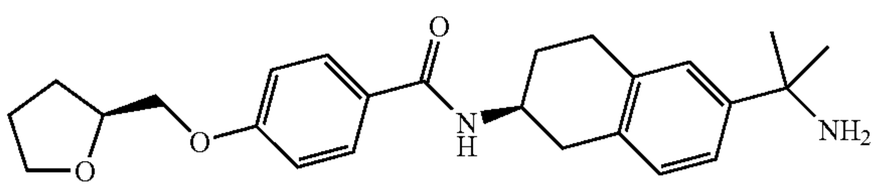
N-((S)-6-{[(E)-(R)-2-Methylpropane-2-sulfinylimino]methyl}-1,2,3,4-tetrahydro-naphthalen-2-yl)-4-[(S)-1-(tetrahydrofuran-2-yl)methoxy]benzamide

Method M-1

A mixture of N-((S)-6-formyl-1,2,3,4-tetrahydronaphthalen-2-yl)-4-[(S)-1-(tetrahydrofuran-2-yl)methoxy]benzamide (1.0 g), (R)-2-methylpropane-2-sulfinic acid amide (0.32 g), pyridinium para-toluenesulfonate (165 mg), copper (II) sulfate (1.0 g; anhydrous) and dichloromethane (10 ml) was stirred for 24 hours. Solid fractions were filtered off and the filtrate was concentrated. The residue was purified by chromatography on silica gel. The product was thus obtained with the molecular weight of 482.65 ($C_{27}H_{34}N_2O_4S$); MS (ESI): 483 (M+H+).

Example 7

N-[(S)-6-(1-Amino-1-methylethyl)-1,2,3,4-tetrahydronaphthalen-2-yl]-4-[(S)-1-(tetrahydrofuran-2-yl)methoxy]benzamide



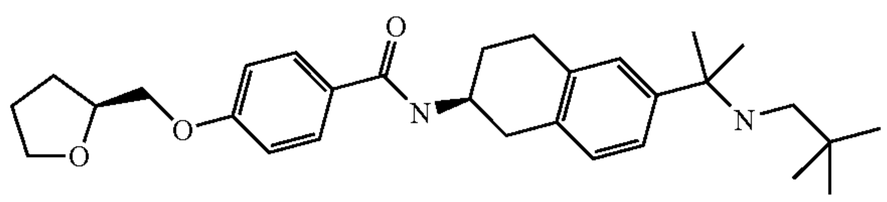
A mixture, cooled to 0° C., of N-[(S)-6-(1-hydroxy-1-methylethyl)-1,2,3,4-tetrahydronaphthalen-2-yl]-4-[(S)-1-(tetrahydrofuran-2-yl)methoxy]benzamide (0.30 g), glacial acetic acid (1 ml) and trimethylsilyl cyanide (145 mg) was admixed dropwise with sulfuric acid (1.2 ml; 96%). The cooling bath was removed and the mixture was stirred for another 12 hours. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic phase was washed with sodium chloride solution, dried over sodium sulfate and concentrated. The residue was taken up in 1,4-dioxane (20 ml) and boiled at reflux with dilute hydrochloric acid for 30 minutes. The reaction mixture was washed with ethyl acetate and basified with concentrated sodium hydroxide solution. Extraction with dichloromethane gave rise to an organic phase which was dried over sodium sulfate and concentrated. (Alternatively, the hydrolysis of the intermediate formamide can also be achieved by boiling with sodium hydroxide solution.) The product was thus obtained with the molecular weight of 408.55 ($C_{25}H_{32}N_2O_3$); MS (ESI): 409 (M+H+).

N-[(S)-6-(1-Hydroxy-1-methylethyl)-1,2,3,4-tetrahydronaphthalen-2-yl]-4-[(S)-1-(tetrahydrofuran-2-yl)methoxy]benzamide

A mixture of N-((S)-6-bromo-1,2,3,4-tetrahydronaphthalen-2-yl)-4-[(S)-1-(tetrahydrofuran-2-yl)methoxy]benzamide (1.0 g) and THF (10 ml) was cooled to −78° C. (dry ice bath), and a solution of methyllithium (2.0 ml; 1.6 M in diethyl ether) was added dropwise. One minute after the addition had ended, a solution of butyllithium (1.4 ml; 2.5 M in toluene) was added dropwise. One minute after the addition had ended, acetone (0.14 g) was added. After warming to room temperature, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic phases were dried over magnesium sulfate and concentrated. The residue was chromatographed on silica gel (eluent: 1:2 heptane/ethyl acetate). The product was thus obtained with the molecular weight of 409.53 ($C_{25}H_{31}NO_4$); MS (ESI): 410 (M+H+).

Example 8-1

N-{(S)-6-[1-(2,2-Dimethylpropylamino)-1-methylethyl]-1,2,3,4-tetrahydro-naphthalen-2-yl}-4-[(S)-1-(tetrahydrofuran-2-yl)methoxy]benzamide



Method H-2

To a mixture of N-[(S)-6-(1-amino-1-methylethyl)-1,2,3,4-tetrahydronaphthalen-2-yl]-4-[(S)-1-(tetrahydrofuran-2-yl)methoxy]benzamide (30 mg), THF (1 ml), methanol (0.5 ml), trimethylacetaldehyde (10 mg) and acetic acid (9 mg) was added polymer-bound sodium cyanoborohydride (0.15 mmol), and the suspension was agitated at room temperature for 12 hours. The polymer was filtered off with suction and the filtrate was concentrated. The residue was purified by preparative HPLC. The product was thus obtained with the molecular weight of 478.68 ($C_{30}H_{42}N_2O_3$); MS (ESI): 479 (M+H+).

In Table 2, examples which have been obtained by reductive alkylation of the appropriate amines by method H-2 with the appropriate carbonyl compounds (aldehyde or ketone) are summarized. If N,N-dialkylations of primary amines are to be achieved by method H-2, 2-3 equivalents of the carbonyl component and correspondingly more sodium cyanoborohydride are used.

TABLE 2

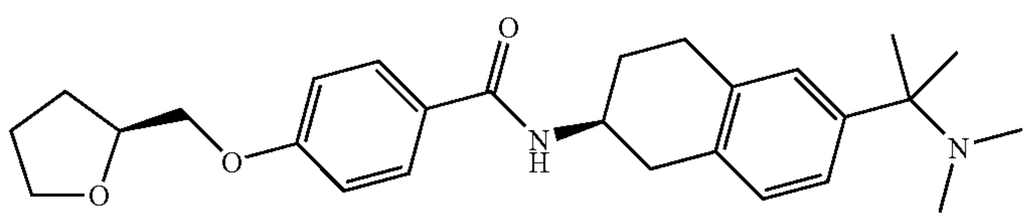
Ex. No.	Structure	Molecular weight	ESI-MS $[M + H]^+$
8-2		436.27	437

TABLE 2-continued

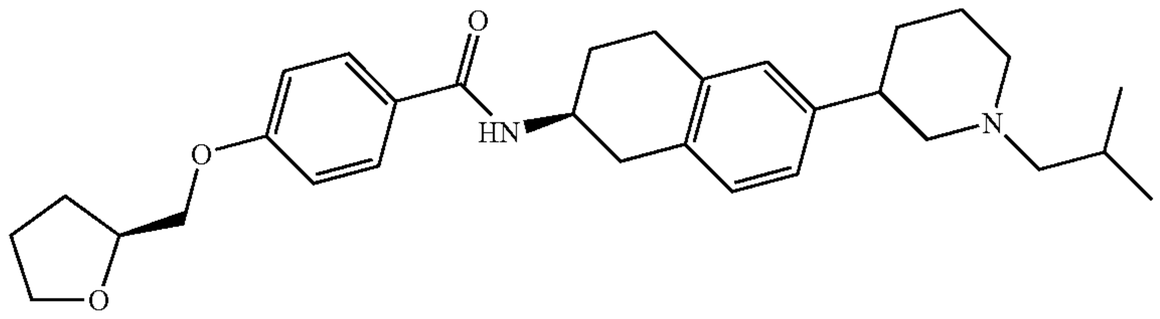
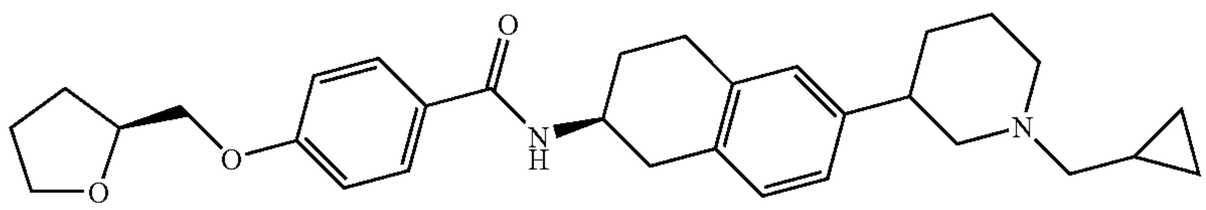
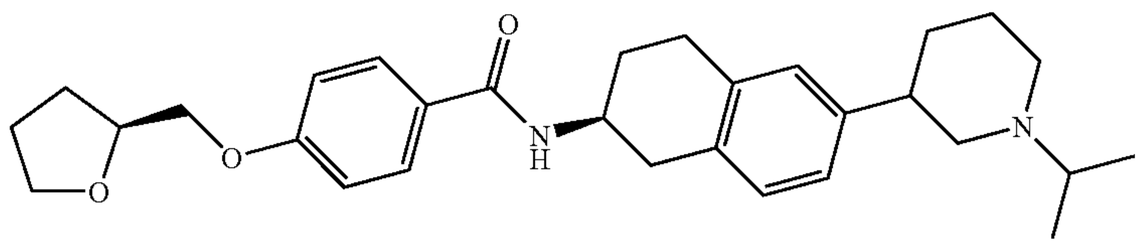
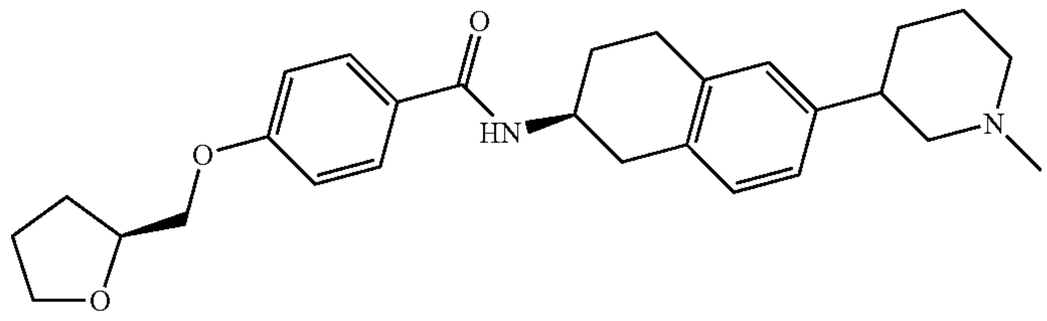
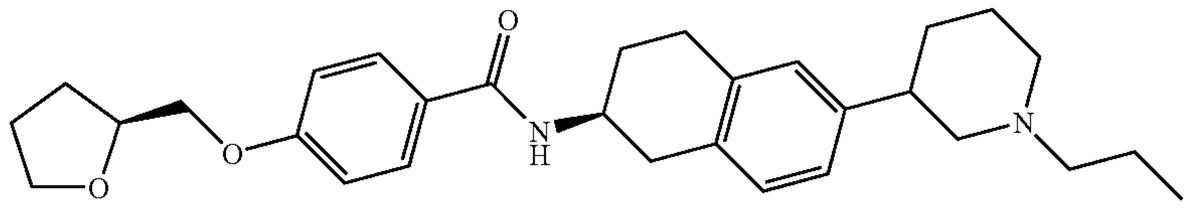
Ex. No.	Structure	Molecular weight	ESI-MS $[M + H]^+$
8-3		490.32	491
8-4		488.30	489
8-5		476.30	477
8-6		448.27	449
8-7		476.30	477
8-8		448.27	449
8-9		488.30	489
8-10		464.30	465

TABLE 2-continued

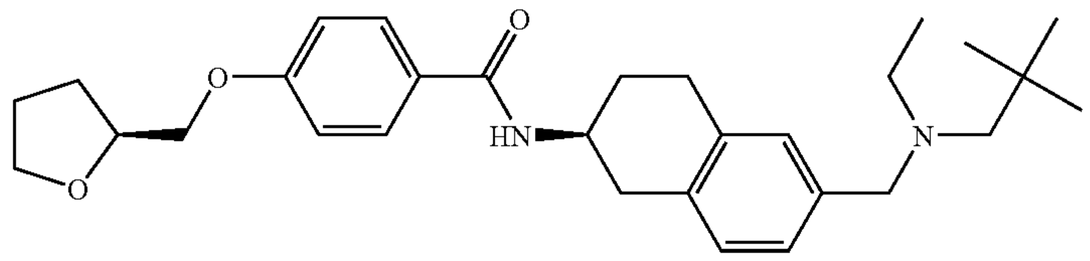
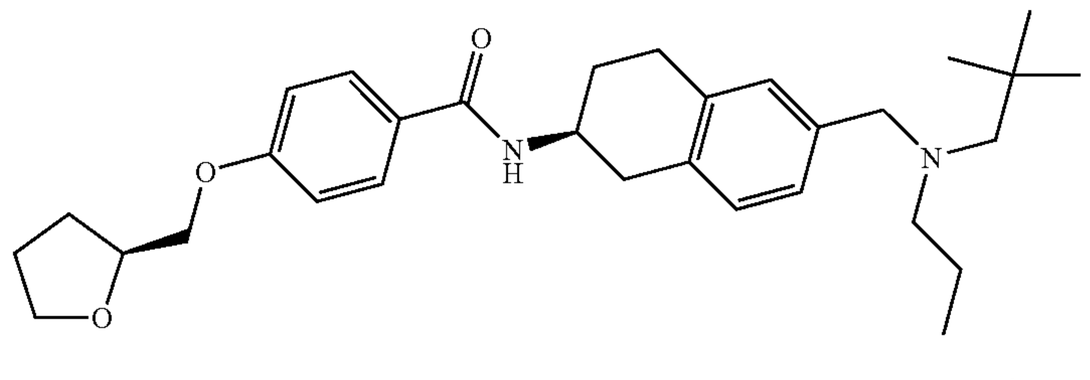
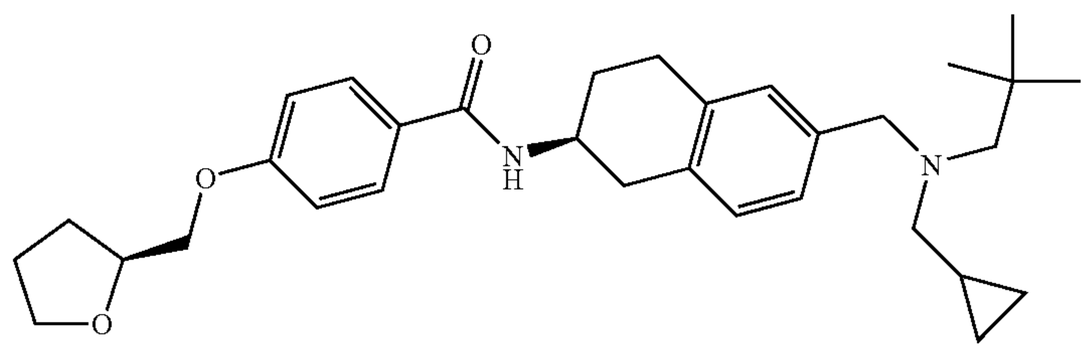
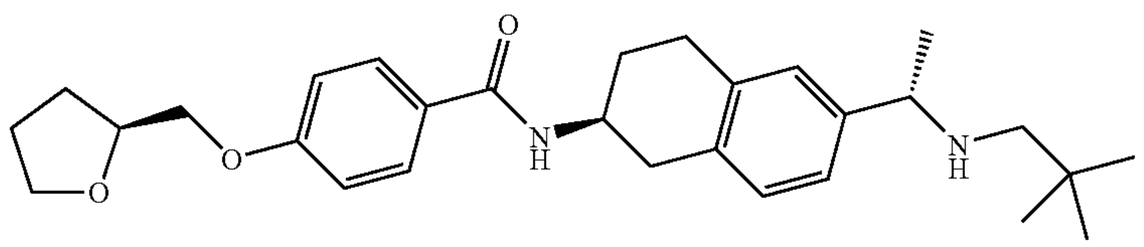
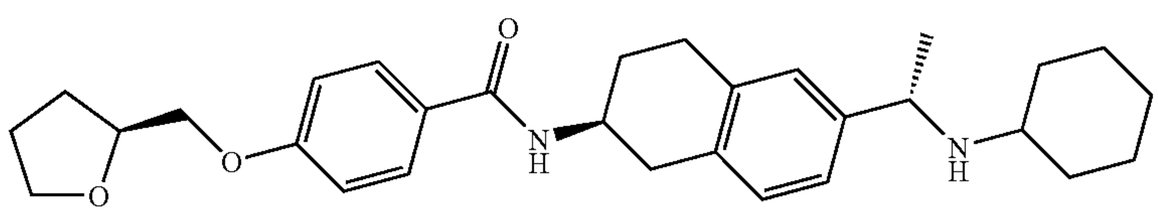
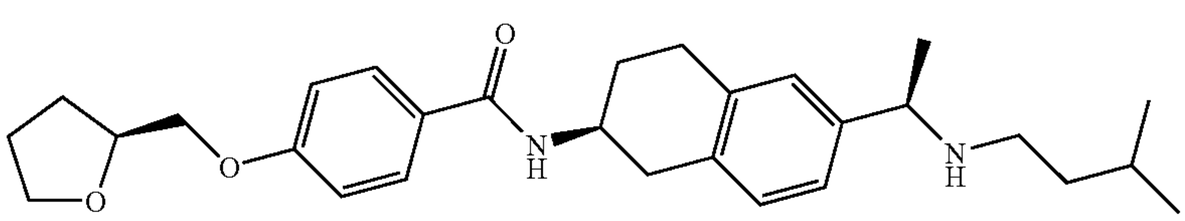
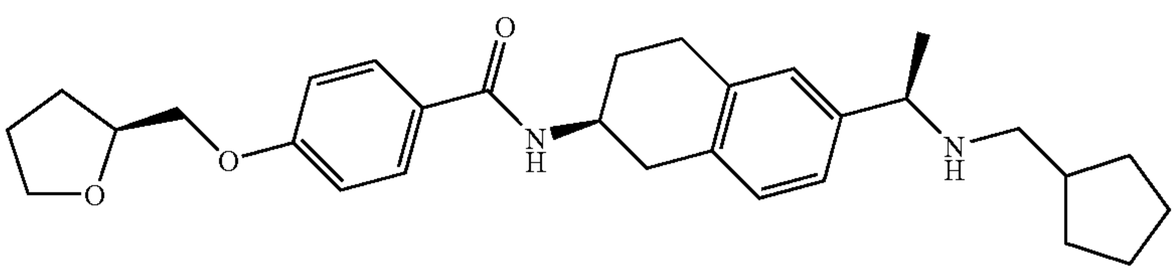
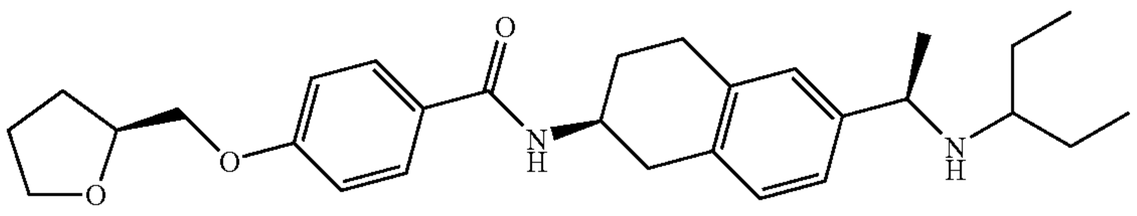
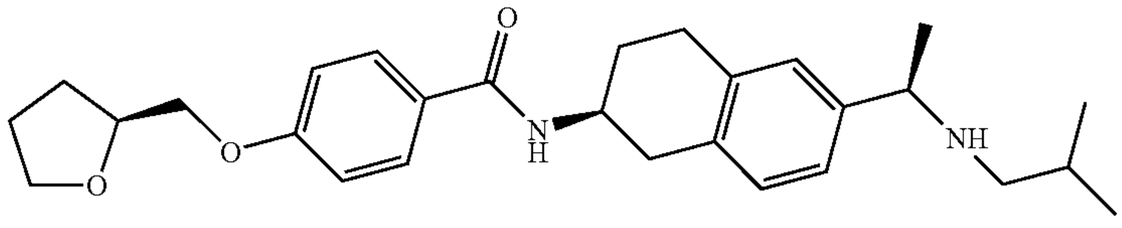
Ex. No.	Structure	Molecular weight	ESI-MS $[M + H]^+$
8-11		478.32	479
8-12		492.34	493
8-13		504.34	505
8-14		464.30	465
8-15		476.30	477
8-16		464.30	465
8-17		476.30	477
8-18		464.30	465
8-19		450.29	451

TABLE 2-continued

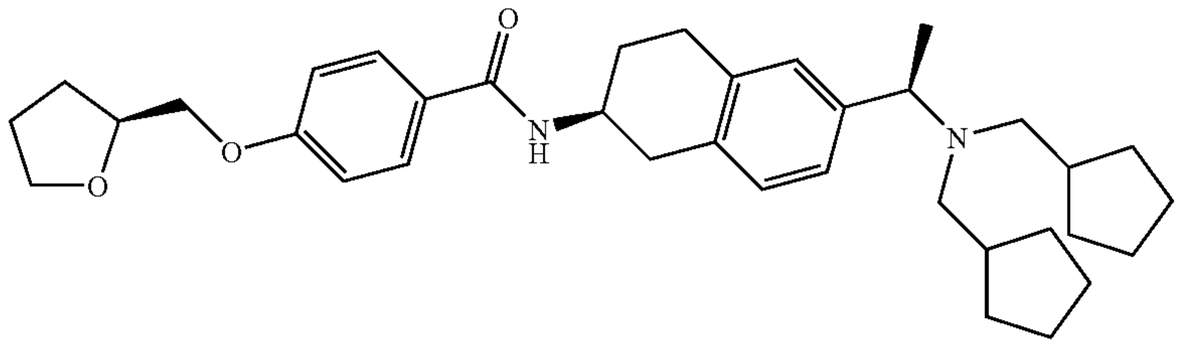
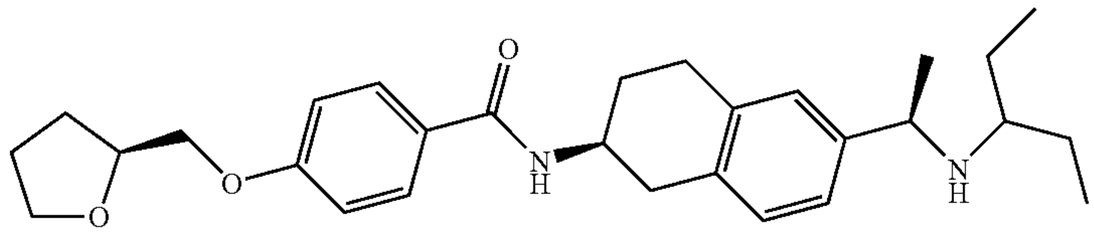
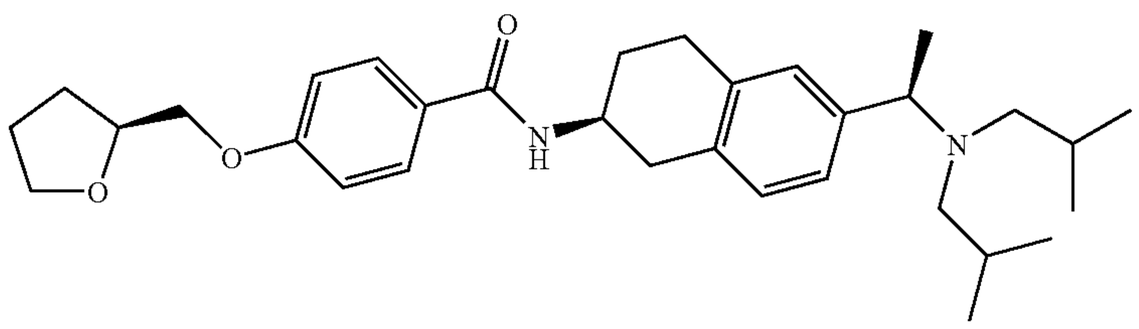
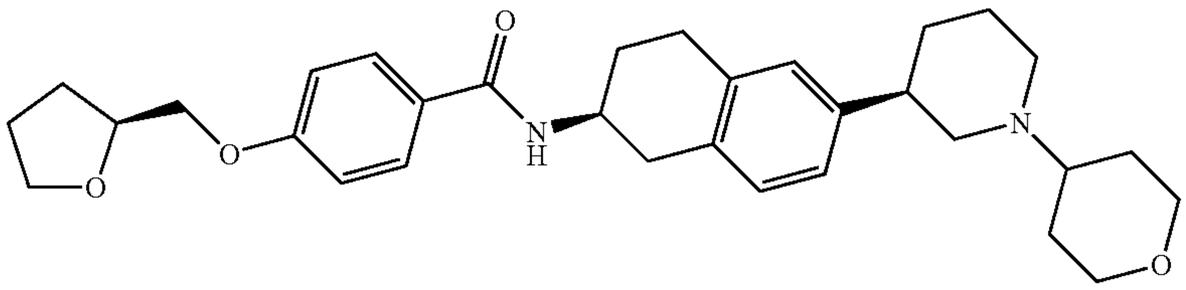
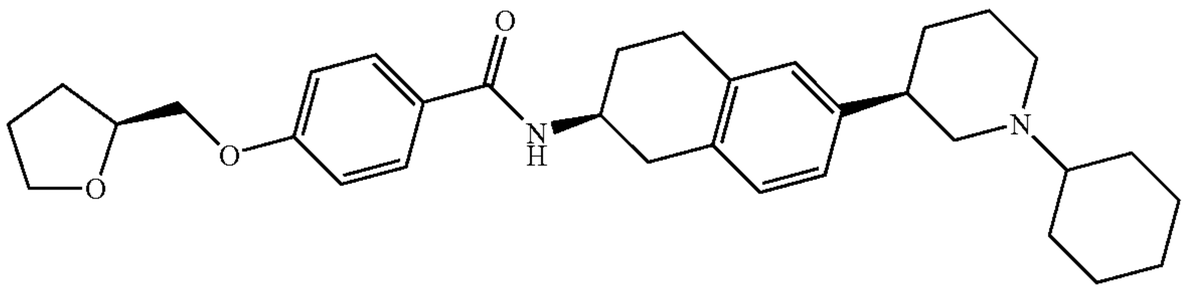
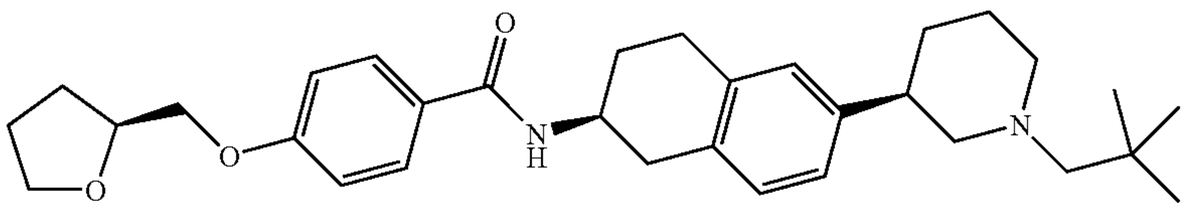
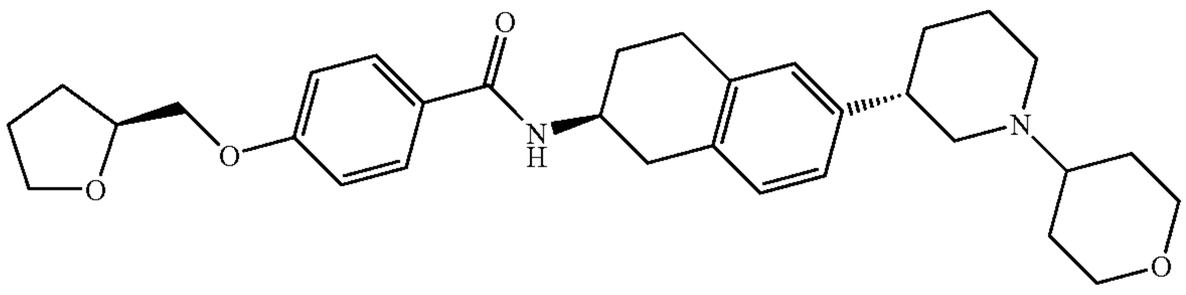
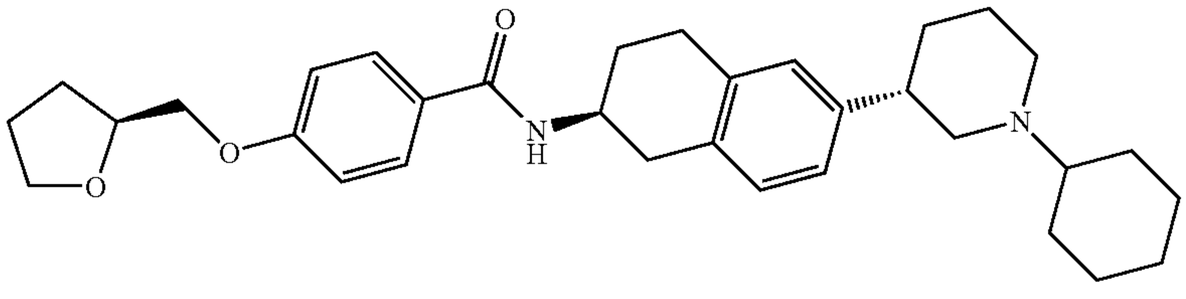
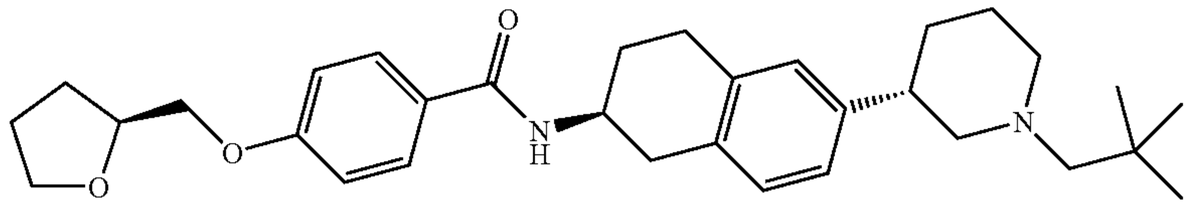
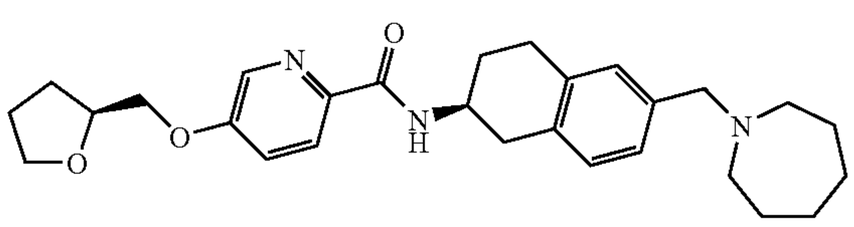
Ex. No.	Structure	Molecular weight	ESI-MS $[M + H]^+$
8-20		558.38	559
8-21		464.30	465
8-22		506.35	507
8-23		518.31	519
8-24		516.34	517
8-25		504.34	505
8-26		518.31	519
8-27		516.34	517

TABLE 2-continued

Ex. No.	Structure	Molecular weight	ESI-MS [M + H]+
8-28		504.34	505

Example 9-1

5-[(S)-1-(Tetrahydrofuran-2-yl)methoxy]pyridine-2-carboxylic acid ((S)-6-azepan-1-ylmethyl-1,2,3,4-tetrahydronaphthalen-2-yl)amide



According to method F, 5-hydroxypyridine-2-carboxylic acid ((S)-6-azepan-1-ylmethyl-1,2,3,4-tetrahydronaphthalen-2-yl)amide was alkylated with methanesulfonic acid (S)-1-(tetrahydrofuran-2-yl)methyl ester (DMF, 12 h, 80° C.). The product was thus obtained with the molecular weight of 463.63 (C28H37N3O3); MS (ESI): 464 (M+H+).

5-Hydroxypyridine-2-carboxylic acid ((S)-6-azepan-1-ylmethyl-1,2,3,4-tetrahydro-naphthalen-2-yl) amide

Method A-2

A mixture of 5-hydroxypyridine-2-carboxylic acid (0.54 g) and DMF (3 ml) was admixed with (3-dimethylaminopropyl)ethylcarbodiimide (EDC; 0.80 g) and benzotriazol-1-ol (HOBt; 0.60 g), and stirred for 5 minutes. Then ethyldiisopropylamine (0.80 ml) and (S)-6-azepan-1-ylmethyl-1,2,3,4-tetrahydronaphthalen-2-ylamine (1.00 g) were added and the mixture was stirred for 12 hours. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic phase was dried over sodium sulfate, filtered and concentrated. The product was thus obtained with the molecular weight of 379.51 (C23H29N3O2); MS (ESI): 380 (M+H+).

In an analogous manner, N-((S)-6-azepan-1-ylmethyl-1,2,3,4-tetrahydronaphthalen-2-yl)-4-hydroxybenzamide was obtained by reacting 4-hydroxybenzoic acid with (S)-6-azepan-1-ylmethyl-1,2,3,4-tetrahydronaphthalen-2-ylamine.

In Table 3, examples which have been prepared by alkylating N-((S)-6-azepan-1-ylmethyl-1,2,3,4-tetrahydronaphthalen-2-yl)-4-hydroxybenzamide according to method F with the appropriate alkylating agents (e.g. bromides, iodides or sulfonic esters) are compiled.

TABLE 3

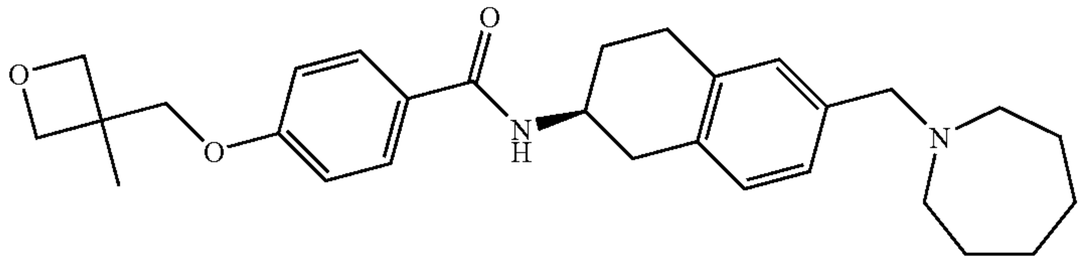
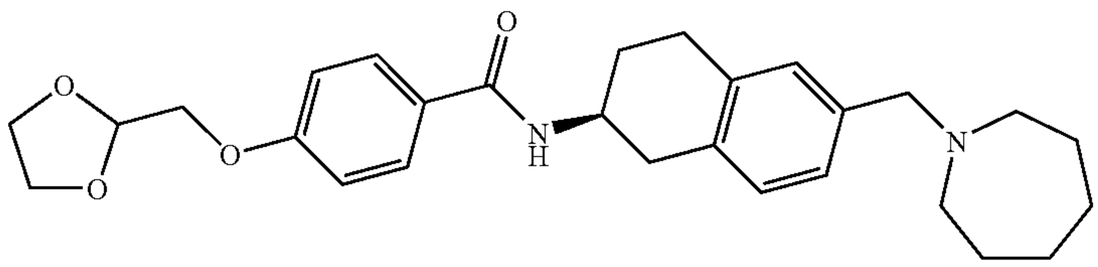
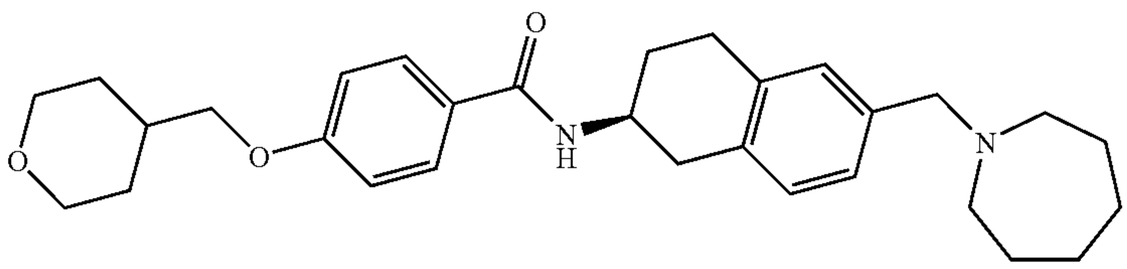
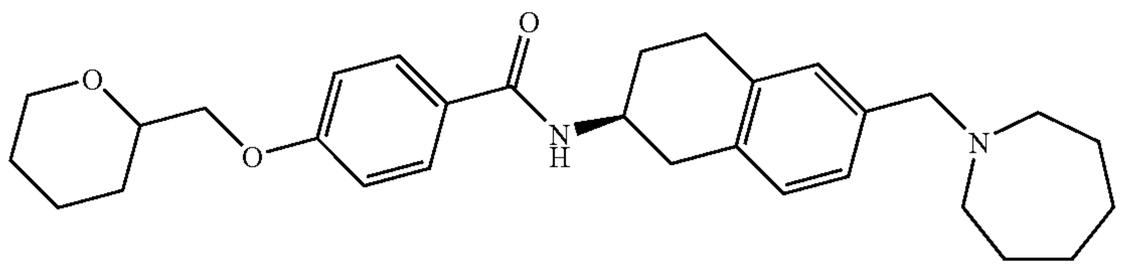
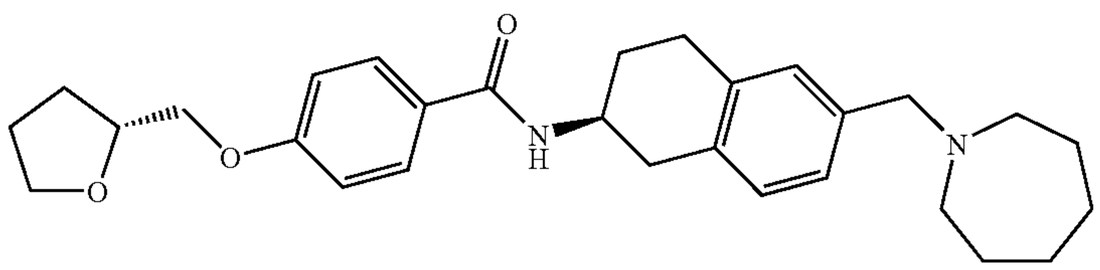
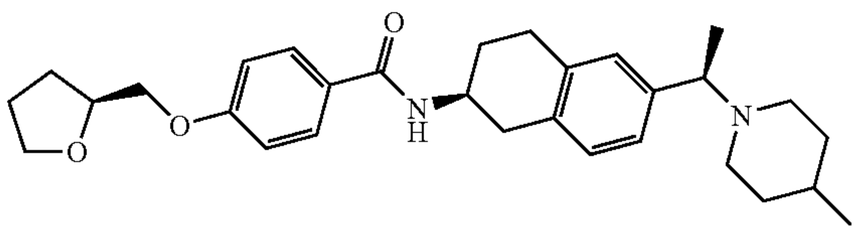
Ex. No.	Structure	Molecular-weight	ESI-MS [M+ H]+
9-2		462.63	463
9-3		464.60	465
9-4		476.66	477

TABLE 3-continued

Ex. No.	Structure	Molecular-weight	ESI-MS [M+ H]+
9-5		476.66	477
9-6		462.64	463

Example 10

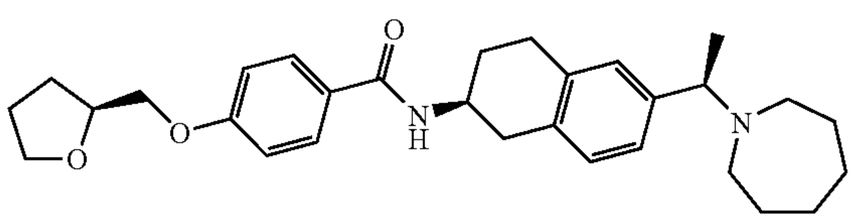
N-{(S)-6-[(R)-1-(4-Methylpiperidin-1-yl)ethyl]-1,2,3,4-tetrahydronaphthalen-2-yl}-4-[(S)-1-(tetrahydrofuran-2-yl)methoxy]benzamide



A mixture of N-[(S)-6-((R)-1-aminoethyl)-1,2,3,4-tetrahydronaphthalen-2-yl]-4-[(S)-1-(tetrahydrofuran-2-yl) methoxy]benzamide (50 mg), 1,5-dibromo-3-methylpentane (31 mg), ethyldiisopropylamine (0.10 ml) and acetonitrile (1 ml) was heated to 40° C. for 8 hours. The cooled reaction mixture was concentrated and the residue was purified by preparative HPLC. The product was thus obtained with the molecular weight of 476.66 (C30H40N2O3); MS (ESI): 477 (M+H+).

Example 11

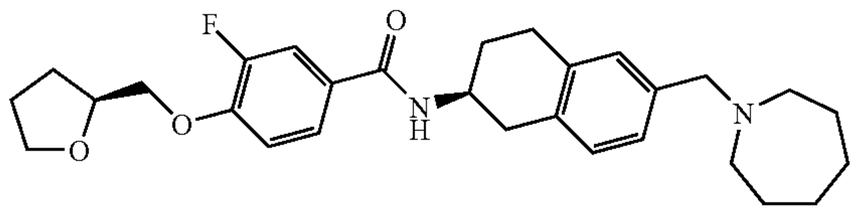
N-[(S)-6-((R)-1-Azepan-1-ylethyl)-1,2,3,4-tetrahydronaphthalen-2-yl]-4-[(S)-1-(tetrahydrofuran-2-yl) methoxy]benzamide



A mixture of N-[(S)-6-((R)-1-aminoethyl)-1,2,3,4-tetrahydronaphthalen-2-yl]-4-[(S)-1-(tetrahydrofuran-2-yl) methoxy]benzamide (50 mg), 1,6-dibromohexane (31 mg), ethyldiisopropylamine (0.10 ml) and acetonitrile (1 ml) was heated to 40° C. for 8 hours. The cooled reaction mixture was concentrated and the residue was purified by preparative HPLC. The product was thus obtained with the molecular weight of 476.66 (C30H40N2O3); MS (ESI): 477 (M+H+).

Example 12

N-((S)-6-Azepan-1-ylmethyl-1,2,3,4-tetrahydronaphthalen-2-yl)-3-fluoro-4-[(S)-1-(tetrahydrofuran-2-yl)methoxy]benzamide



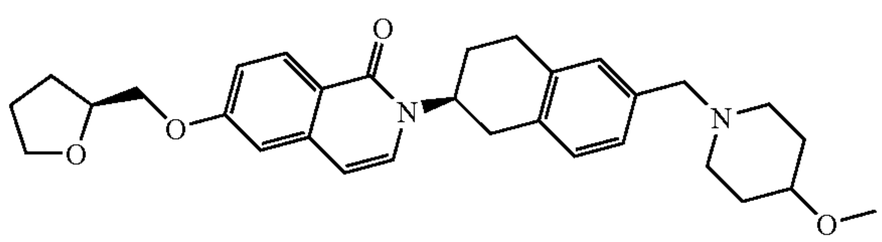
According to method A-2,3-fluoro-4-[(S)-1-(tetrahydrofuran-2-yl)methoxy]benzoic acid was reacted with (S)-6-azepan-1-ylmethyl-1,2,3,4-tetrahydronaphthalen-2-ylamine. The product was thus obtained with the molecular weight of 480.63 (C29H37FN2O3); MS (ESI): 481 (M+H+).

3-Fluoro-4-[(S)-1-(tetrahydrofuran-2-yl)methoxy] benzoic acid

According to method F, 3-fluoro-4-hydroxybenzoic acid ethyl ester was alkylated with methanesulfonic acid (S)-1-(tetrahydrofuran-2-yl)methyl ester, and the reaction product was hydrolyzed by method E. The product was thus obtained with the molecular weight of 240.23 (C12H13FO4); MS (ESI): 241 (M+H+).

Example 13

2-[(S)-6-(4-Methoxypiperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-2-yl]-6-[(S)-1-(tetrahydrofuran-2-yl)methoxy]-2H-isoquinolin-1-one



A mixture of 6-[(S)-1-(tetrahydrofuran-2-yl)methoxy]isochromen-1-one (50 mg), NMP (0.2 ml) and (S)-6-(4-methoxypiperidin-1-ylmethyl)-1,2,3,4-tetrahydro-naphthalen-2-ylamine (55 mg) was heated to 220° C. in a microwave reactor for 3×30 minutes. The cooled reaction mixture was purified by preparative HPLC. The product was thus obtained with the molecular weight of 502.66 (C31H38N2O4); MS (ESI): 503 (M+H+).

6-[(S)-1-(Tetrahydrofuran-2-yl)methoxy]isochromen-1-one

To a solution of 6-hydroxyisochromen-1-one (2 g) in DMF (50 ml) were added methanesulfonic acid (S)-1-(tetrahydrofuran-2-yl)methyl ester (2.7 g) and cesium carbonate (12 g), and the mixture was stirred at 80° C. for 7 hours. After water had been added, the mixture was extracted with dichloromethane. The organic phases were dried over magnesium sulfate and concentrated. The product was thus obtained with the molecular weight of 246.27 (C14H14O4); MS (ESI): 247 (M+H+).

6-Hydroxyisochromen-1-one

Method N

To a solution of 6-methoxyisochromen-1-one (9.3 g) in dichloromethane (300 ml) was added, at 0° C., a solution of boron tribromide (1 M in dichloromethane, 130 ml), and the mixture was stirred at room temperature for 16 hours. After sodium carbonate solution had been added, the mixture was washed with ethyl acetate. The aqueous phase was acidified with 2 N HCl and extracted with ethyl acetate. The organic phases were dried over magnesium sulfate and concentrated. The residue was chromatographed on silica gel. The product was thus obtained with the molecular weight of 162.15 (C9H6O3); MS (ESI): 163 (M+H+).

6-Methoxyisochromen-1-one

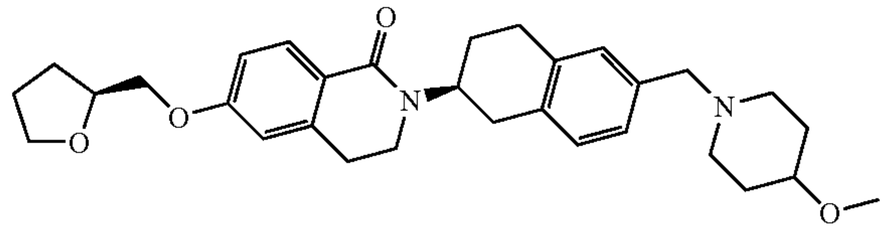
A solution of 6-methoxyisochroman-1-one (15.1 g), N-bromosuccinimide (NBS; 27 g) and benzoyl peroxide (500 mg) in tetrachloromethane (250 ml) was heated to reflux while irradiating with light for 3 hours. The mixture was filtered and the filtrate was concentrated. The residue was dissolved in triethylamine (100 ml) and stirred at room temperature for 48 hours. The reaction mixture was partitioned between water and ethyl acetate and adjusted to pH 1 with concentrated hydrochloric acid. The organic phase was removed, dried over magnesium sulfate and concentrated. The residue was chromatographed on silica gel. The product was thus obtained with the molecular weight of 176.17 (C10H8O3); MS (ESI): 177 (M+H+).

6-Methoxyisochroman-1-one

To a solution of diisopropylamine (33.5 ml) in dry THF (190 ml) was added dropwise, at −78° C., n-butyllithium (1.6 M solution in hexane, 145.9 ml). Subsequently, the reaction mixture was warmed to room temperature for 5 minutes and then cooled again to −78° C., and a solution of 4-methoxy-2-methylbenzoic acid (10 g) in dry THF (210 ml) was added dropwise. After stirring at this temperature for 10 minutes, paraformaldehyde (7 g) was added. The reaction mixture was then allowed to come to room temperature and stirred at this temperature for 4 hours. The reaction mixture was admixed with water, then the THF was removed under reduced pressure and then the aqueous phase was extracted with diethyl ether. The aqueous phase was acidified with conc. HCl, and the resulting precipitate was filtered off and washed repeatedly with water. The product was thus obtained with the molecular weight of 178.06 (C10H10O3); MS (ESI): 179 (M+H+).

Example 14

2-[(S)-6-(4-Methoxypiperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-2-yl]-6-[(S)-1-(tetrahydrofuran-2-yl)methoxy]-3,4-dihydro-2H-isoquinolin-1-one



According to method F, 6-hydroxy-2-[(S)-6-(4-methoxypiperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-2-yl]-3,4-dihydro-2H-isoquinolin-1-one was alkylated with methanesulfonic acid (S)-1-(tetrahydrofuran-2-yl)methyl ester. The product was thus obtained with the molecular weight of 504.68 (C31H40N2O4); MS (ESI): 505 (M+H+).

6-Hydroxy-2-[(S)-6-(4-methoxypiperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-2-yl]-3,4-dihydro-2H-isoquinolin-1-one

A mixture of 6-methoxy-2-[(S)-6-(4-methoxypiperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-2-yl]-3,4-dihydro-2H-isoquinolin-1-one (0.59 g), NMP (2 ml), thiophenol (150 mg) and potassium carbonate (235 mg) was heated to 210° C. in a microwave reactor for 40 minutes. The cooled reaction mixture was purified by chromatography on silica gel (eluent: 9:1 dichloromethane/methanol). The product was thus obtained with the molecular weight of 420.56 (C26H32N2O3); MS (ESI): 421 (M+H+).

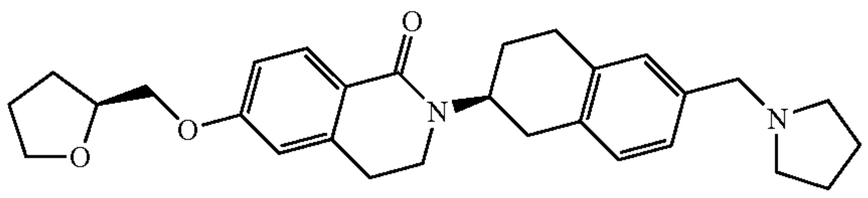
6-Methoxy-2-[(S)-6-(4-methoxypiperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-2-yl]-3,4-dihydro-2H-isoquinolin-1-one

Method O

A mixture of 6-methoxyisochroman-1-one (1.30 g) and thionyl chloride (0.87 g) was admixed with one drop of DMF and heated to reflux for 5 hours. Volatile fractions were distilled off. The residue was taken up in THF (2 ml) and added dropwise to a mixture, cooled to 0° C., of (S)-6-(4-methoxypiperidin-1-ylmethyl)-1,2,3,4-tetrahydronaphthalen-2-ylamine (2.00 g), THF (20 ml) and triethylamine (1.0 ml). After 15 minutes, potassium tert-butoxide (0.82 g) was added and the cooling bath was removed after 30 minutes. After a further 12 hours at room temperature, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic phase was dried over sodium sulfate and concentrated. The residue was purified by preparative HPLC. The product was thus obtained with the molecular weight of 434.58 (C27H34N2O3); MS (ESI): 435 (M+H+).

Example 15-1

2-((S)-6-Pyrrolidin-1-ylmethyl-1,2,3,4-tetrahydronaphthalen-2-yl)-6-[(S)-1-(tetrahydrofuran-2-yl)methoxy]-3,4-dihydro-2H-isoquinolin-1-one



According to method H-1, (S)-6-{1-oxo-6-[(S)-1-(tetrahydrofuran-2-yl)methoxy]-3,4-dihydro-1H-isoquinolin-2-yl}-5,6,7,8-tetrahydronaphthalene-2-carbaldehyde was reacted with pyrrolidine. The product was thus obtained with the molecular weight of 460.62 ($C_{29}H_{36}N_2O_3$); MS (ESI): 461 (M+H+).

(S)-6-{1-oxo-6-[(S)-1-(tetrahydrofuran-2-yl)methoxy]-3,4-dihydro-1H-isoquinolin-2-yl}-5,6,7,8-tetrahydronaphthalene-2-carbaldehyde

Method P

A mixture of 2-((S)-6-bromo-1,2,3,4-tetrahydronaphthalen-2-yl)-6-[(S)-1-(tetra-hydrofuran-2-yl)methoxy]-3,4-dihydro-2H-isoquinolin-1-one (1.10 g), palladium(II) acetate (16.2 mg), butyldi-1-adamantylphosphine (77 mg), TMEDA (0.27 ml) and toluene (22 ml) was heated to 120° C. in an autoclave under a hydrogen/carbon monoxide atmosphere for 14 hours. The cooled reaction mixture was diluted with ethyl acetate and washed first with dilute hydrochloric acid and then with sodium hydrogen carbonate solution. The organic phase was dried over sodium sulfate and concentrated. The residue was purified by preparative HPLC. The product was thus obtained with the molecular weight of 405.50 ($C_{25}H_{27}NO_4$); MS (ESI): 406 (M+H+).

2-((S)-6-Bromo-1,2,3,4-tetrahydronaphthalen-2-yl)-6-[(S)-1-(tetrahydrofuran-2-yl)methoxy]-3,4-dihydro-2H-isoquinolin-1-one

According to method O, 6-[(S)-1-(tetrahydrofuran-2-yl)methoxy]isochroman-1-one was reacted with (S)-6-bromo-1,2,3,4-tetrahydronaphthalen-2-ylamine (J. Org. Chem. 1995, 60, 4324). The product was thus obtained with the molecular weight of 456.38 ($C_{24}H_{26}BrNO_3$); MS (ESI): 456 (M+H+).

6-[(S)-1-(Tetrahydrofuran-2-yl)methoxy]isochroman-1-one

A mixture of 6-hydroxyisochroman-1-one (332 mg), methanesulfonic acid (S)-1-(tetrahydrofuran-2-yl)methyl ester (284 mg), cesium carbonate (1.28 g) and DMF (8 ml) was heated to 70° C. for 7 hours. The cooled reaction mixture was partitioned between water and ethyl acetate. The organic phase was dried and concentrated. The crude product was purified by chromatography on silica gel. The product was thus obtained with the molecular weight of 248.28 ($C_{14}H_{16}O_4$); MS (ESI): 249 (M+H+).

6-Hydroxyisochroman-1-one

According to method N, 6-methoxyisochroman-1-one was treated with boron tribromide.

In Table 4, examples which have been obtained by reacting (S)-6-{1-oxo-6-[(S)-1-(tetrahydrofuran-2-yl)methoxy]-3,4-dihydro-1H-isoquinolin-2-yl}-5,6,7,8-tetrahydronaphthalene-2-carbaldehyde with amines according to method H-1 are compiled.

TABLE 4

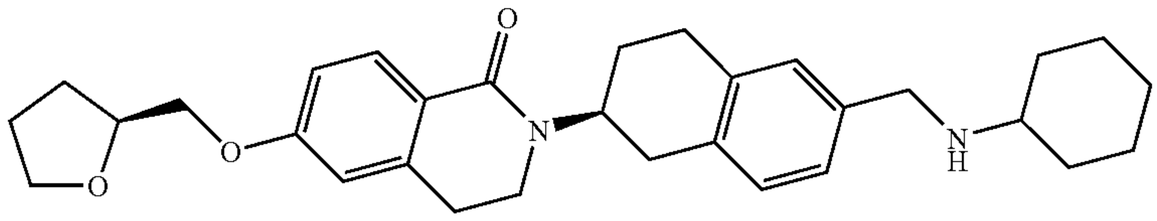
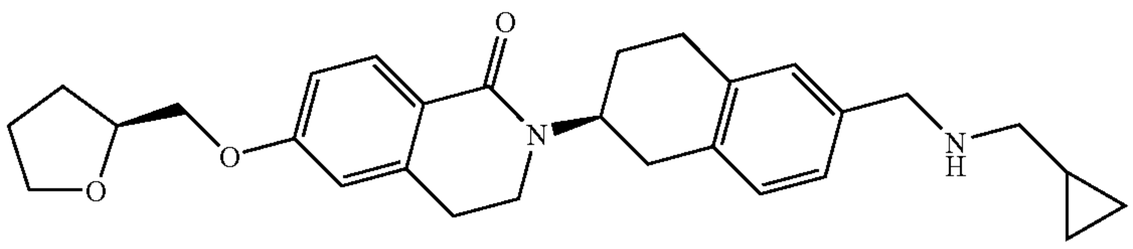
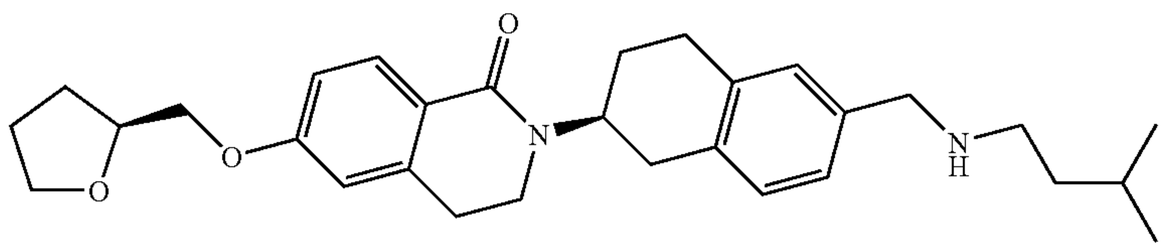
Ex. No.	Structure	Molecular weight	ESI-MS $[M+H]^+$
15-2		488.68	489
15-3		460.62	461
15-4		476.66	477

TABLE 4-continued

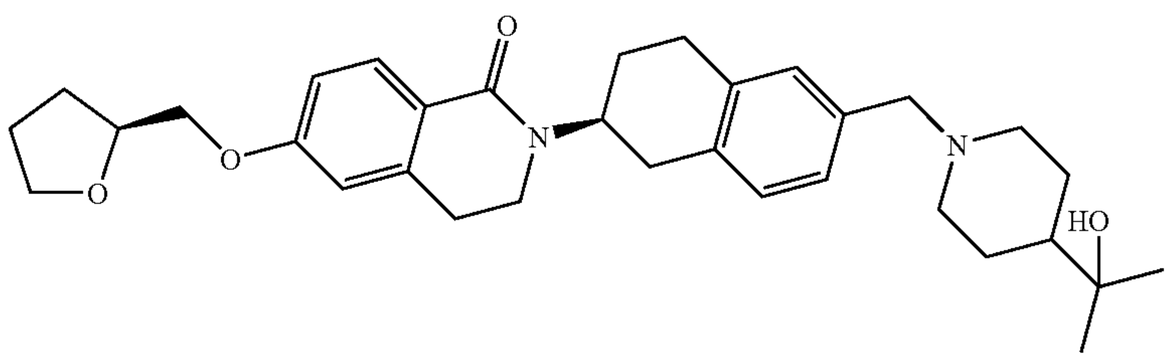
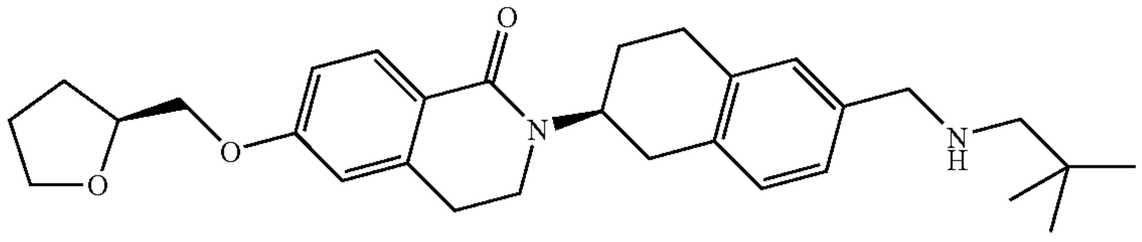
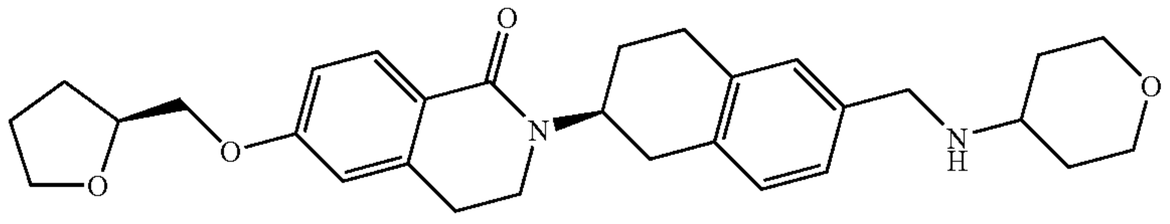
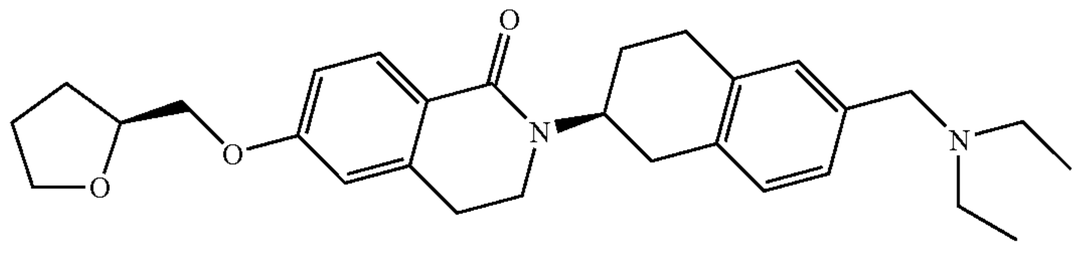
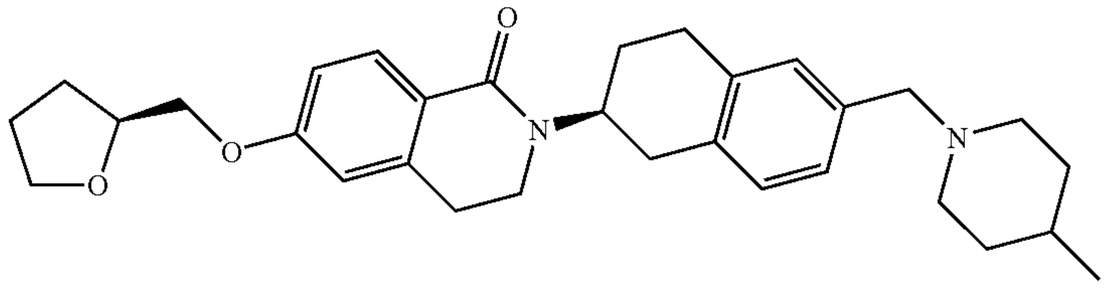
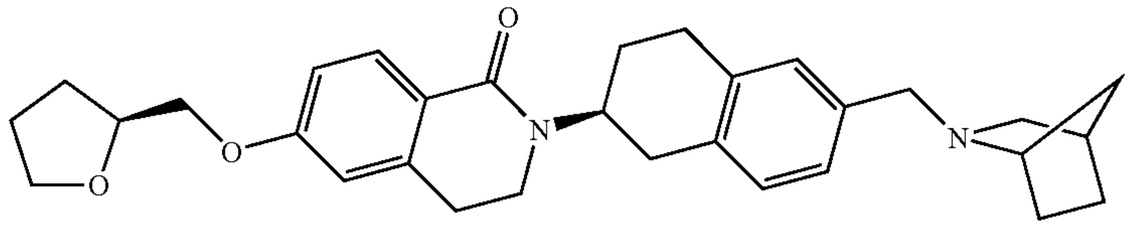
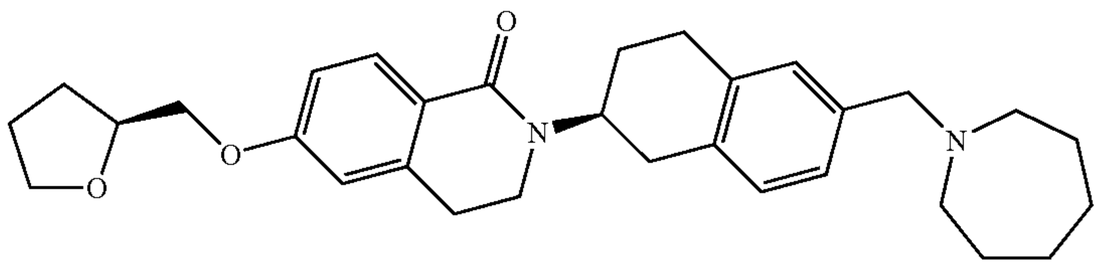
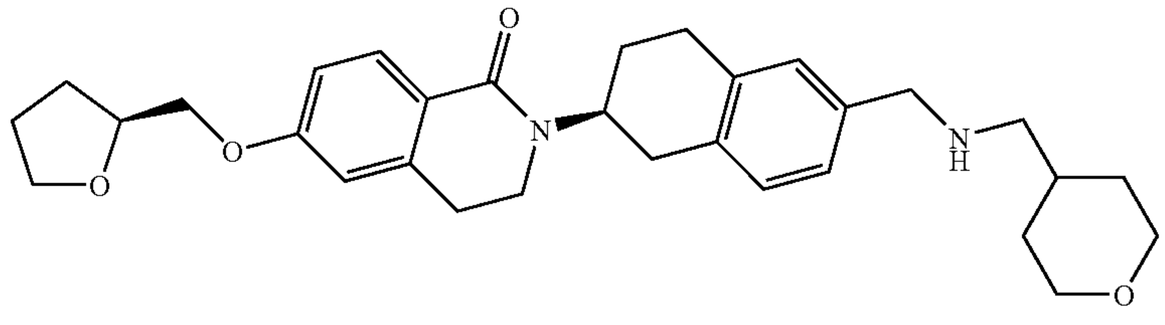
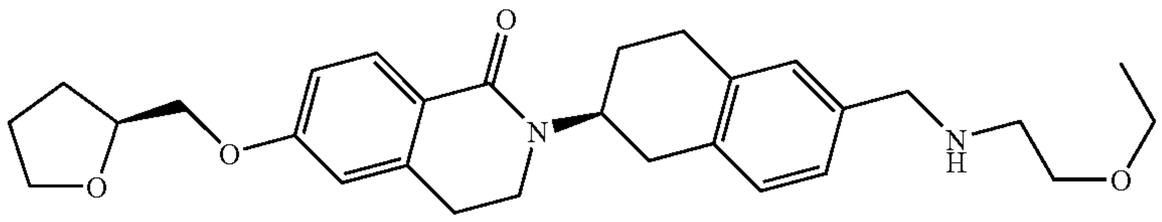
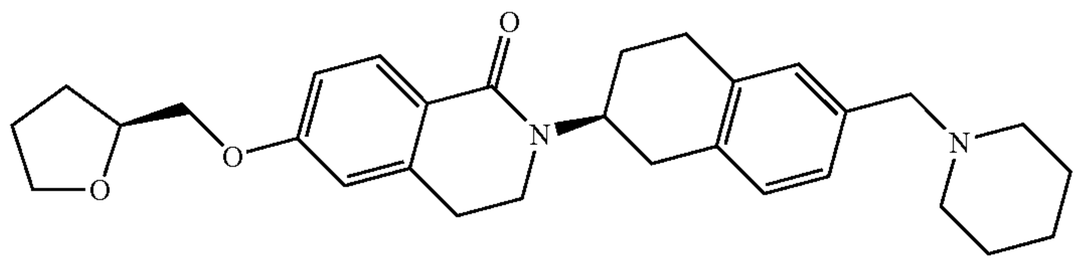
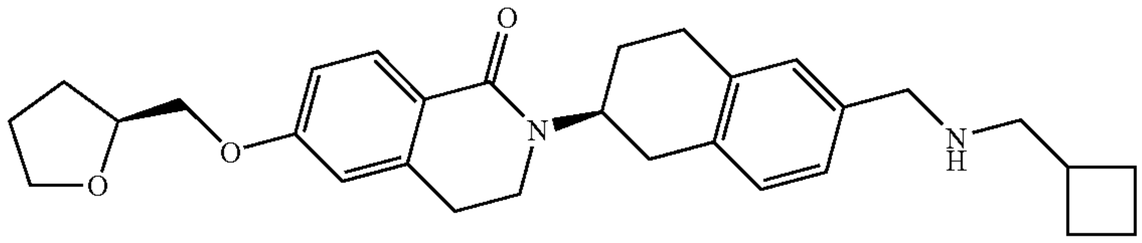
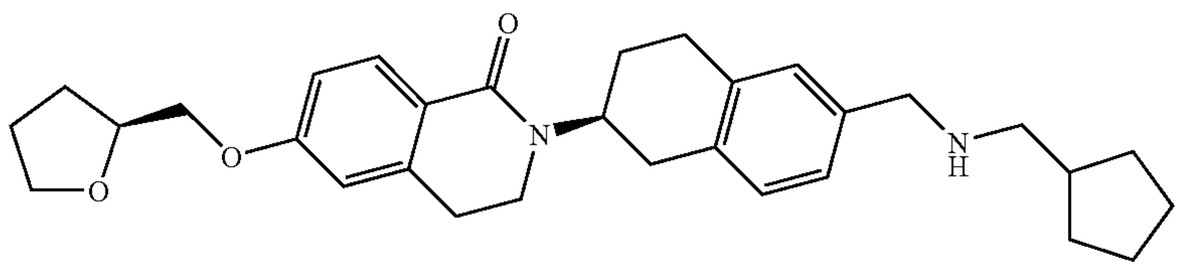
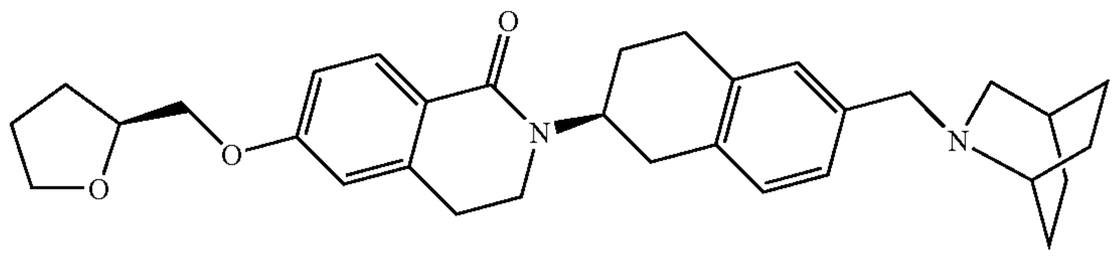
Ex. No.	Structure	Molecular weight	ESI-MS $[M+H]^+$
15-5		532.73	533
15-6		476.66	477
15-7		490.65	491
15-8		462.64	463
15-9		488.68	489
15-10		486.66	487
15-11		488.68	489
15-12		504.68	505

TABLE 4-continued

Ex. No.	Structure	Molecular weight	ESI-MS $[M+H]^+$
15-13		478.64	479
15-14		474.65	475
15-15		474.65	475
15-16		488.68	489
15-17		500.69	501

In Table 5, results which have been obtained in the above-described calcium mobilization assay are summarized for illustrative purposes.

TABLE 5

Ex. No.	IC50/ μM
1	0.09
2	0.67
3-2	3.29
3-14	0.10
3-26	0.36
3-32	0.13
3-33	0.27
3-34	0.10
3-37	0.34
3-40	0.18
3-44	0.31
3-48	0.21
3-51	0.19
3-61	0.30
3-64	0.18
3-71	0.75
3-72	1.85
3-77	0.12
3-84	0.17
3-86	0.12
3-100	0.33
3-103	0.20
3-120	2.41
3-135	0.15
3-166	0.11
3-194	0.09
3-195	0.11
8-1	0.24
8-3	0.23
8-8	0.18
8-16	0.12
8-26	0.23
9-2	1.28
9-3	0.17
9-4	0.44
9-5	0.31
10	0.11
12	0.30
13	1.40
14	0.63

In Table 6, results which have been determined in the above-described hERG inhibition assay and in the test for kinetic solubility are compiled for illustrative purposes. It is found that inventive compounds advantageously combine low hERG inhibition with a high solubility in aqueous systems at a physiologically relevant pH of 7.4. In contrast, prior art compounds frequently exhibit a lower solubility. For

example, for example No. 110 ((S)-enantiomer) from US2005/0075324, a solubility of <10 μm was found. The publication Bioorg. Med. Chem. Lett. 2007, 17, 814-818 (table footnote on page 817) also describes the sparing solubility of the prior art compounds.

TABLE 6

Ex. No.	hERG Inh. IC50/μM	Neph. sol. pH 7.4/μM
1	>30	>500
3-6	>10	>500
3-34	>30	50
3-83	>30	>500
3-154	>10	>500
3-166	>10	450
14	>10	>500

Table 7 lists examples with an aminochromane base skeleton, which can be prepared by the processes described above by way of example. In order to obtain inventive compounds, for example, by the process described in Scheme 2 or by way of example in Example 3-1, it is possible to proceed, for example, from 7-bromochroman-3-one, which is supplied commercially (Anichem LLC; 195 Black Horse Lane; North Brunswick, N.J., 08902; USA) or by the following route:

7-Bromochroman-3-one

A mixture of 4-bromo-2-hydroxybenzaldehyde (20 g), acrylonitrile (26.4 g) and DABCO (0.78 g) was heated at reflux for 8 hours. After cooling, the reaction mixture was diluted with ethyl acetate and washed with water. The organic phase was concentrated and the residue was filtered through silica gel. The 7-bromo-2H-chromene-3-carbonitrile thus obtained (7.5 g) was boiled at reflux with sodium hydroxide solution (10.2 g of sodium hydroxide in 100 ml of water) for 8 hours. The cooled reaction mixture was washed with methyl tert-butyl ether, acidified with hydrochloric acid and extracted with ethyl acetate. Concentration of the organic phase gave 7-bromo-2H-chromene-3-carboxylic acid. This acid (3.0 g) was heated to 85° C. with DPPA (3.2 g), triethylamine (1.6 ml) and toluene (30 ml) for 12 hours. Then hydrochloric acid (6 N) was added and the mixture was heated to reflux for 2 hours. The cooled reaction mixture was extracted with ethyl acetate and the organic phase was concentrated. The product was thus obtained with the molecular weight of 227.06 ($C_9H_7BrO_2$); MS (ESI): 227 ($M+H^+$).

The examples of Table 7 serve to illustrate further possible embodiments of the invention, without restricting it.

TABLE 7

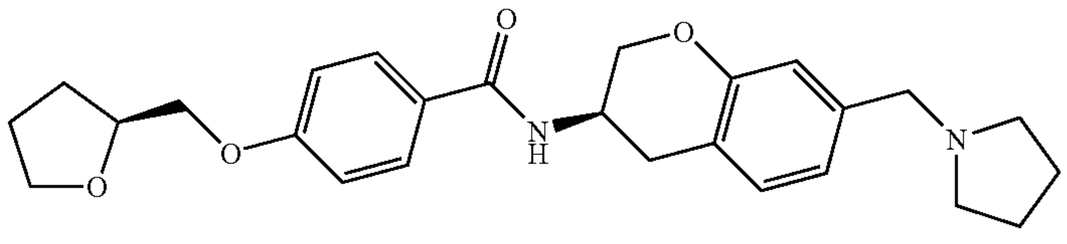
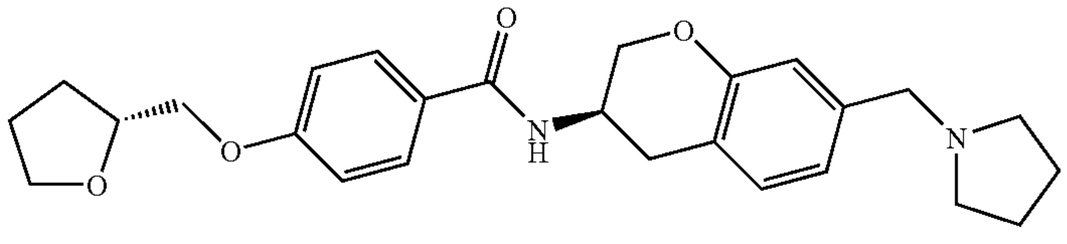
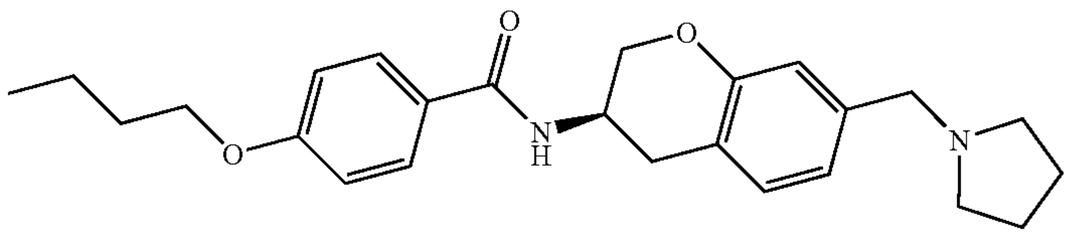
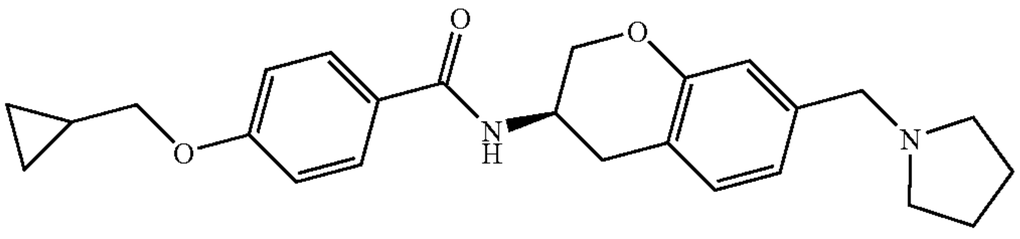
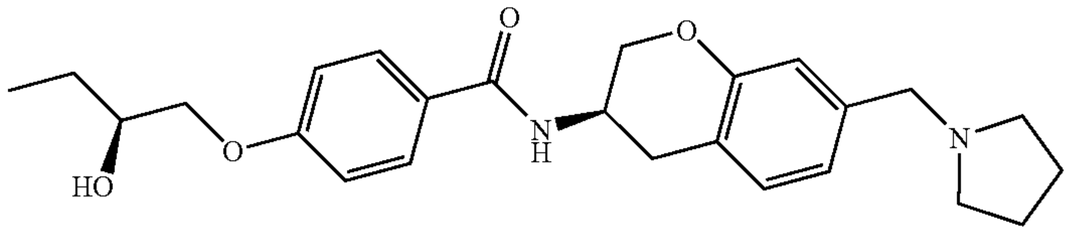
Ex. No.	Structure	Molecular-weight	Calc. $[M + H]^+$
1-1		436.55	437
1-2		436.55	437
1-3		408.54	409
1-4		406.53	407
1-5		424.54	425

TABLE 7-continued

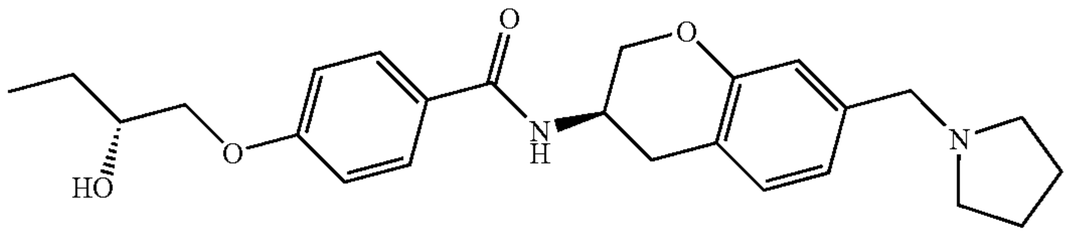
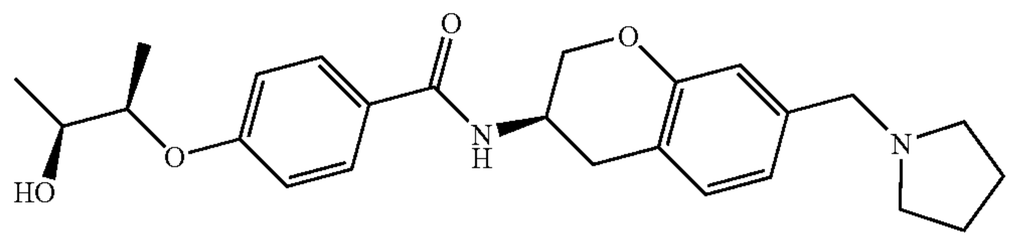
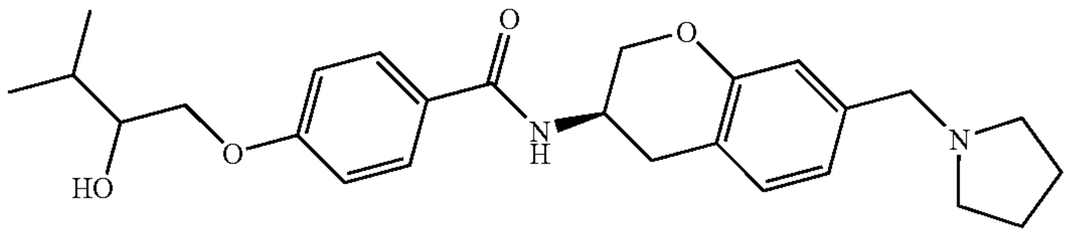
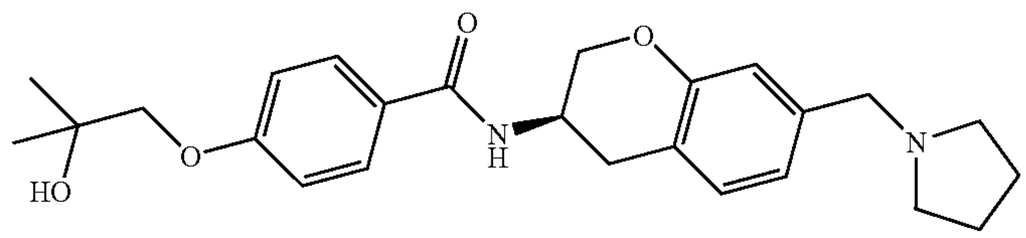
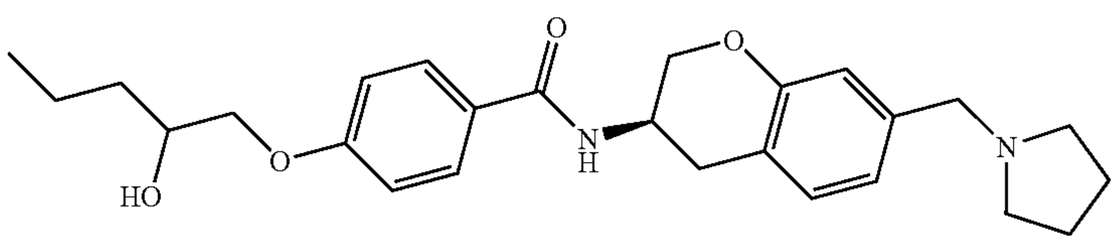
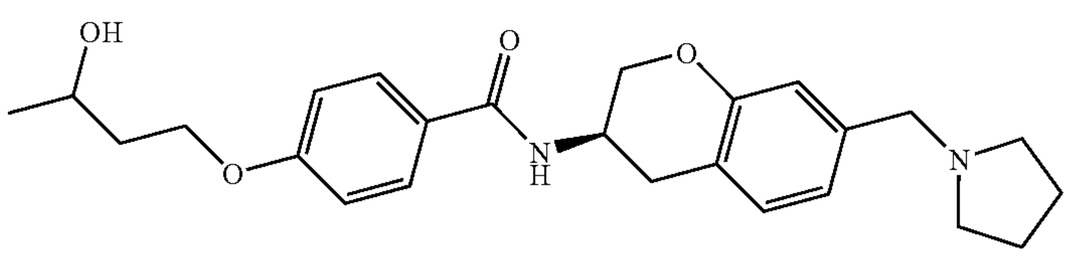
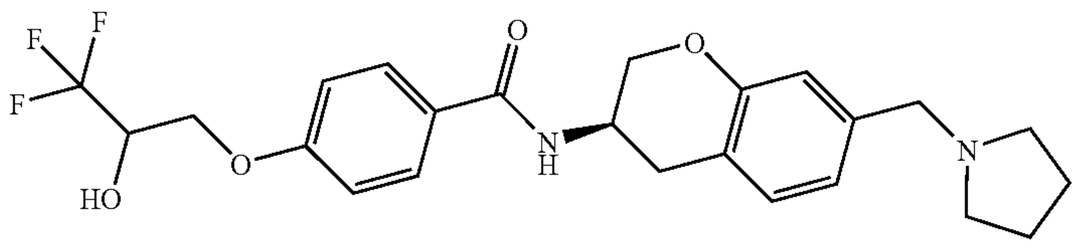
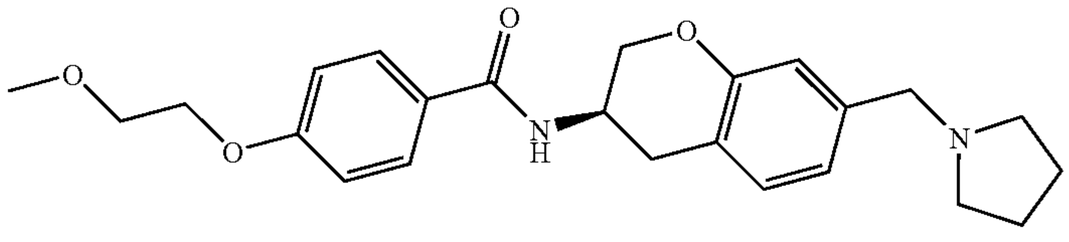
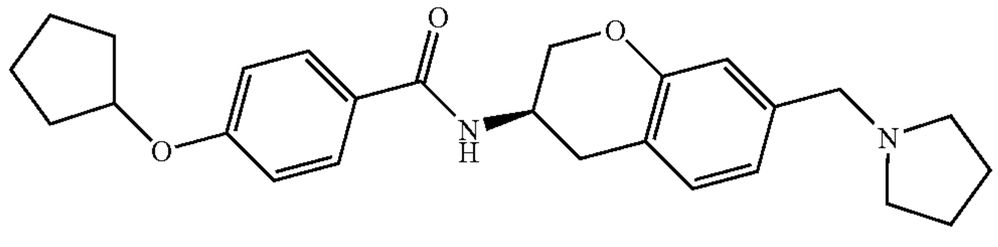
Ex. No.	Structure	Molecular-weight	Calc. $[M + H]^+$
1-6		424.54	425
1-7		424.54	425
1-8		438.57	439
1-9		424.54	425
1-10		438.57	439
1-11		424.54	425
1-12		464.48	464
1-13		410.51	411
1-14		420.55	421

TABLE 7-continued

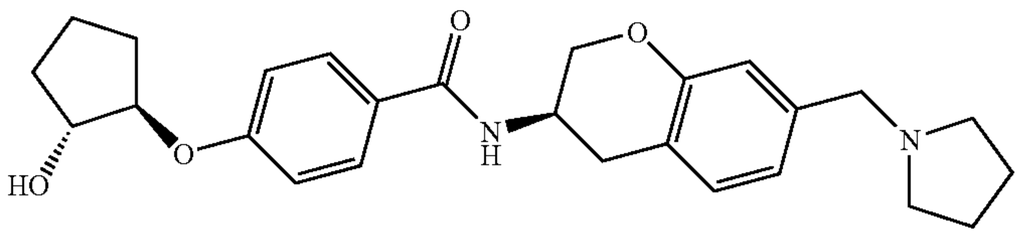
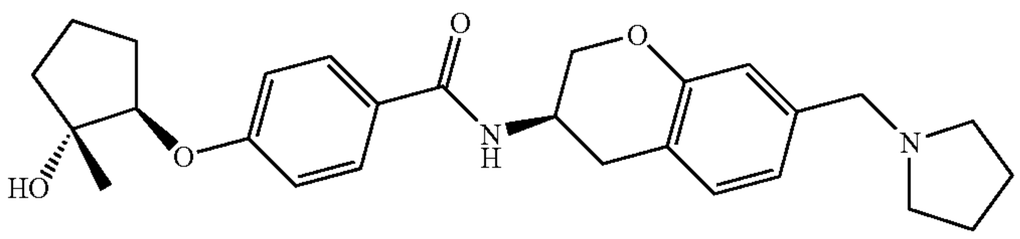
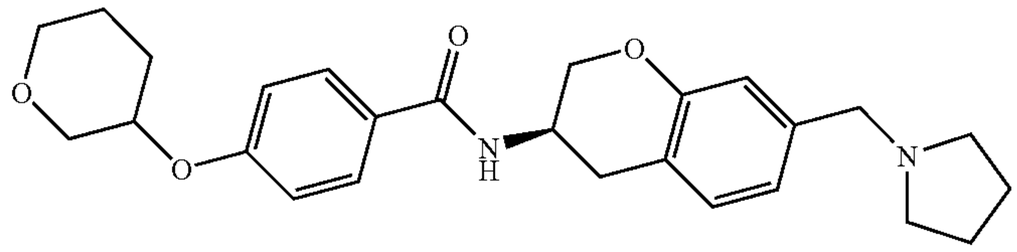
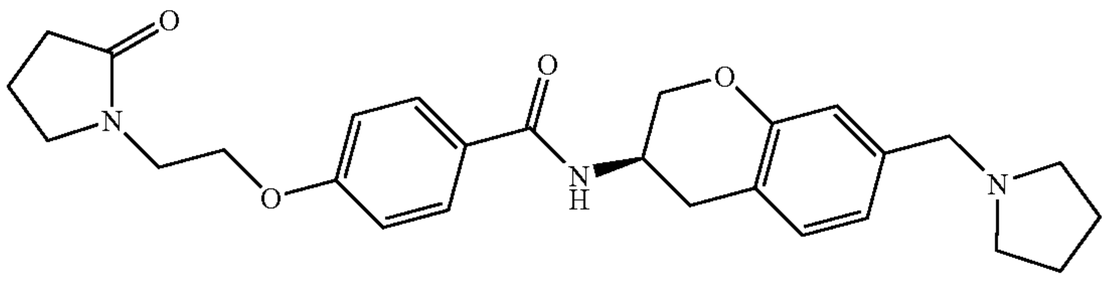
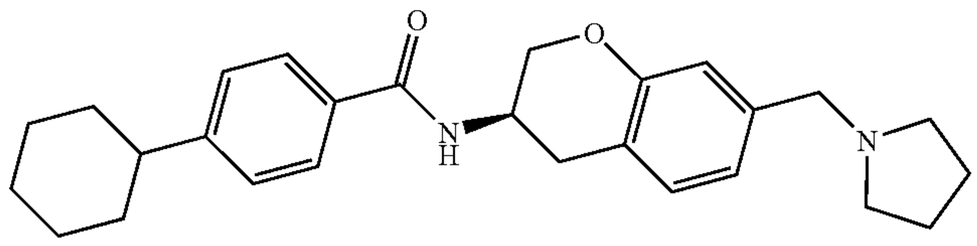
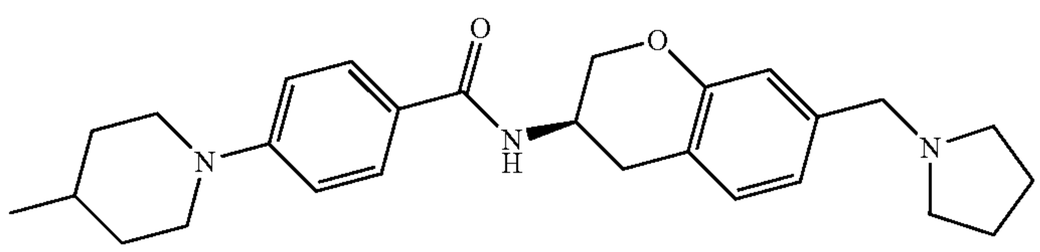
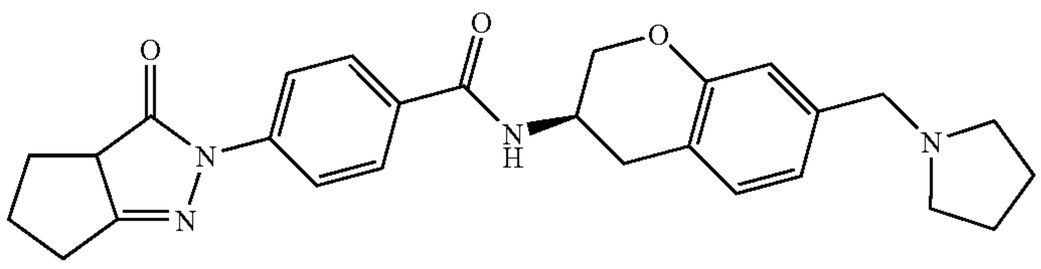
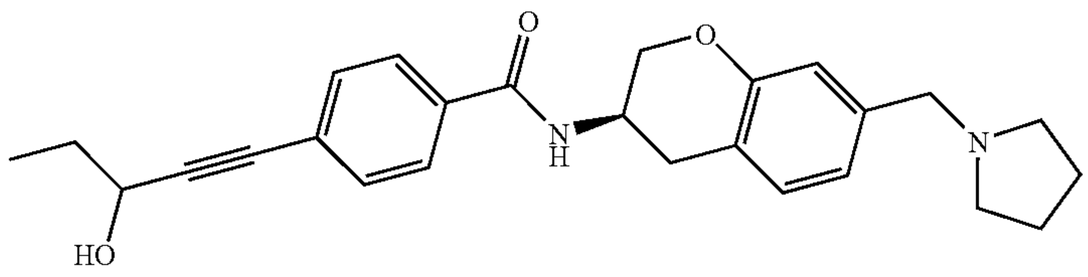
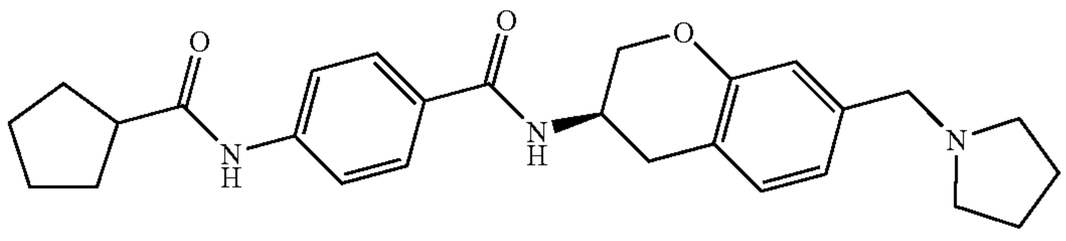
Ex. No.	Structure	Molecular-weight	Calc. $[M + H]^+$
1-15		436.55	437
1-16		450.58	451
1-17		436.55	437
1-18		463.58	464
1-19		418.58	419
1-20		433.60	434
1-21		458.56	459
1-22		418.54	419
1-23		447.58	448

TABLE 7-continued

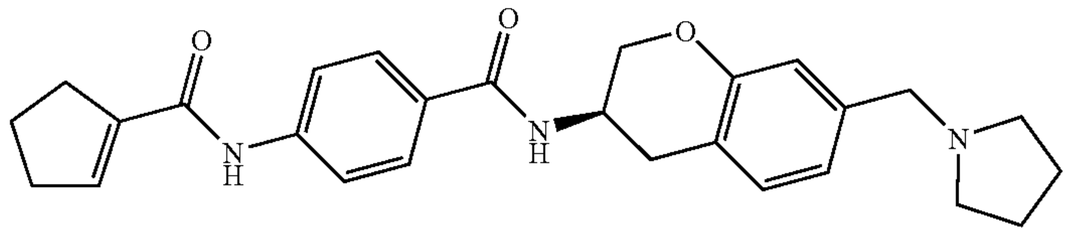
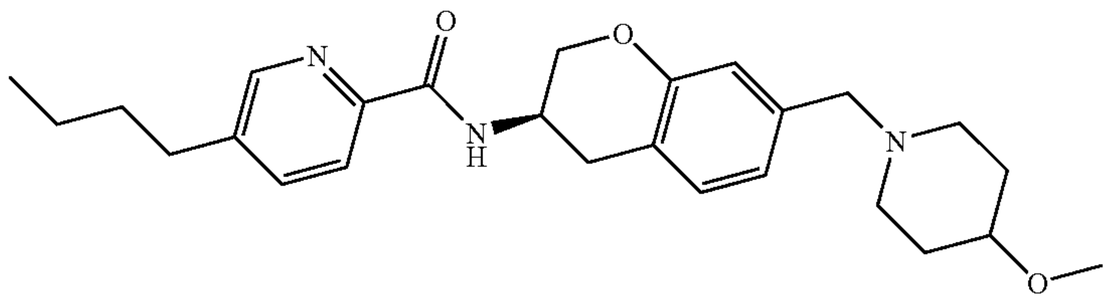
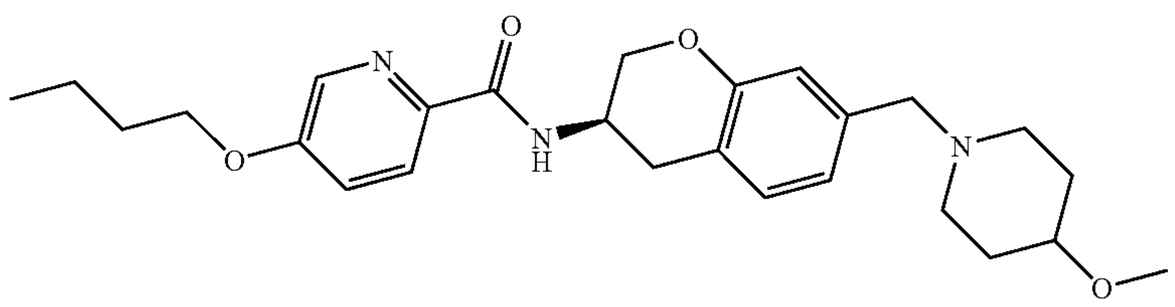
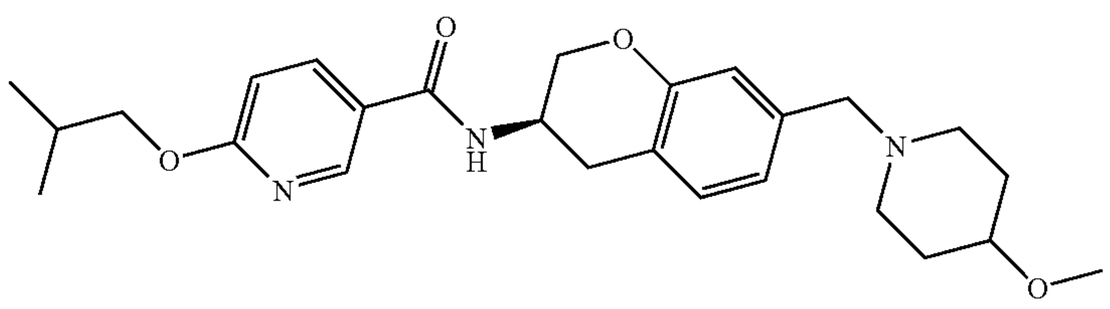
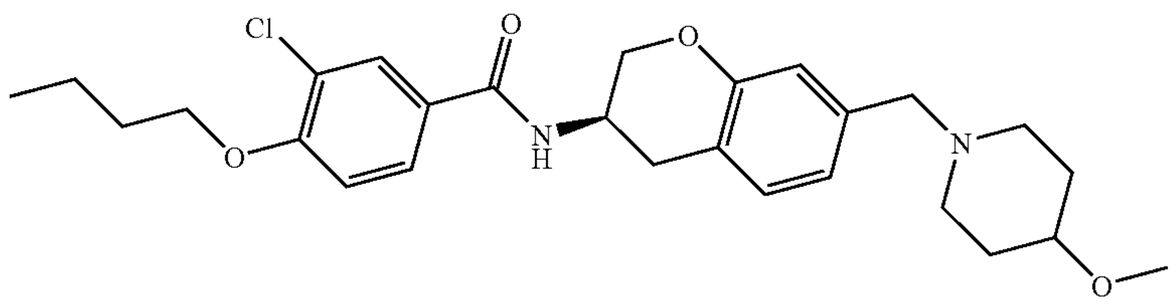
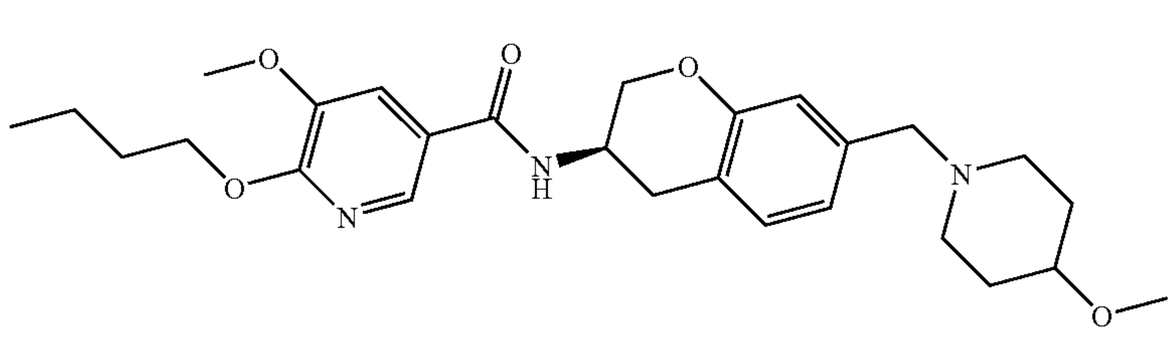
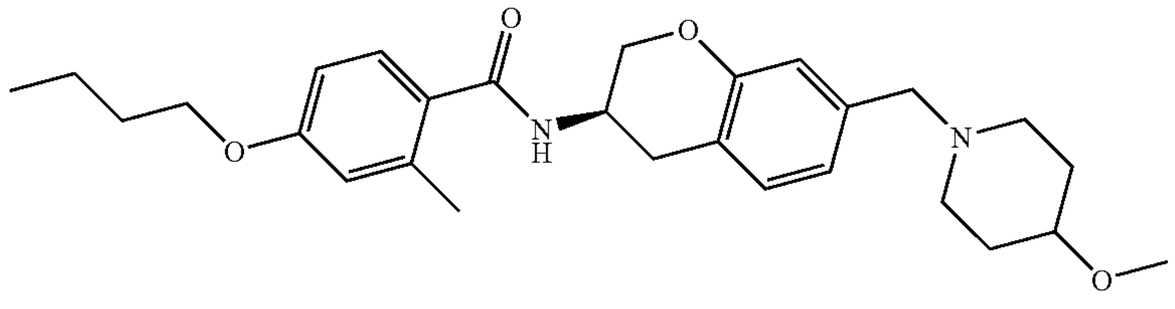
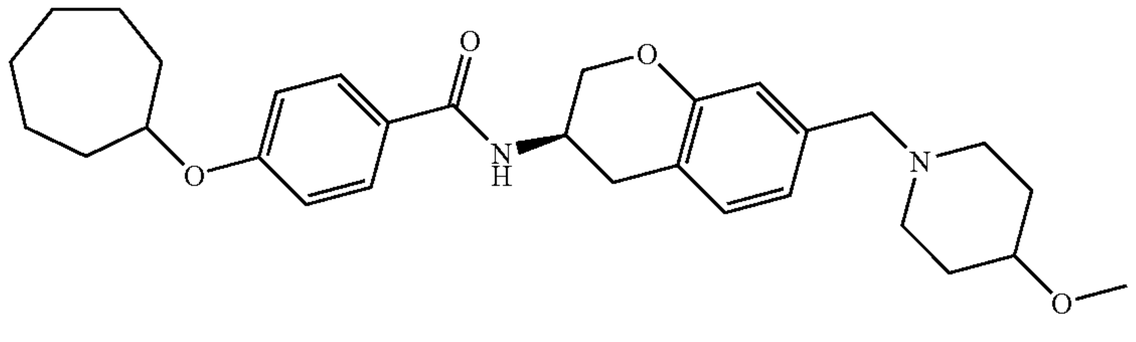
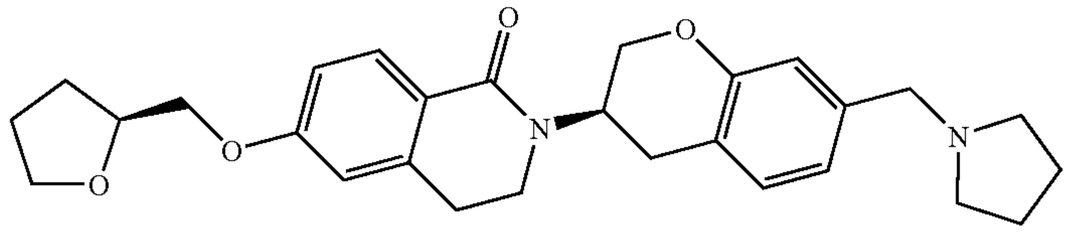
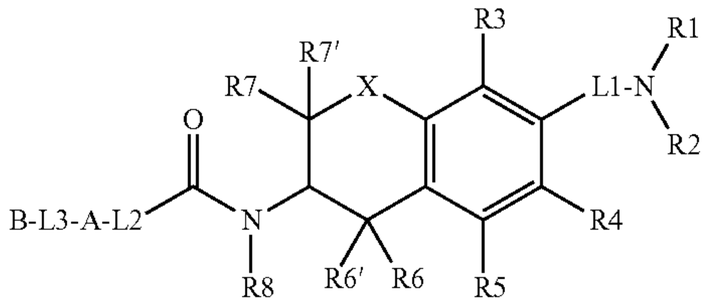
Ex. No.	Structure	Molecular-weight	Calc. $[M + H]^+$
1-24		445.56	446
1-25		437.58	438
1-26		453.58	454
1-27		453.58	454
1-28		487.04	487
1-29		482.62	483
1-30		466.62	467
1-31		492.66	493

TABLE 7-continued

Ex. No.	Structure	Molecular-weight	Calc. $[M + H]^+$
1-32		462.59	463

We claim:

1. A compound of formula I



wherein:

R1 and R2 taken together with the nitrogen atom to which they are attached form a 4- to 10-membered mono-, bi- or spirocyclic ring which, apart from the nitrogen atom, may include from 0 to 3 additional heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur, wherein the ring is optionally substituted by F, Cl, Br, CF_3, CN, $(C_1$-$C_6)$-alkyl, $(C_3$-$C_8)$-cycloalkyl, O—$(C_1$-$C_8)$-alkyl, $(C_1$-$C_4)$-alkoxy-$(C_1$-$C_4)$-alkyl, hydroxy-$(C_1$-$C_6)$-alkyl, oxo, CO(R18), CON(R19)(R20), hydroxyl, COO(R21), N(R22)CO$(C_1$-$C_6)$-alkyl, N(R23)(R24) or $SO_2(C_1$-$C_6)$-alkyl;

R18, R19, R20, R21, R22, R23 and R24, are each independently H or $(C_1$-$C_6)$-alkyl;

or

R23 and R24 taken together with the nitrogen atom to which they are attached form a 5-6-membered ring which, apart from the nitrogen atom, may also include 0-1 further heteroatoms selected from the group consisting of NH, N—$(C_1$-$C_6)$-alkyl, oxygen and sulfur;

L1 is C(R34)(R35) or C(R36)(R37)C(R38)(R39);

optionally, R1 may be joined to one of the R34, R35, R36, R37, R38 or R39 radicals, so as to form a 5-6-membered ring;

R34, R35, R36, R37, R38 and R39 are each independently H or $(C_1$-$C_8)$-alkyl;

R3, R4 and R5 are each independently H, F, Cl, Br, I, OH, CF_3, NO_2, CN, OCF_3, O—$(C_1$-$C_6)$-alkyl, S—$(C_1$-$C_6)$-alkyl, O—$(C_1$-$C_4)$-alkoxy-$(C_1$-$C_4)$-alkyl, $(C_1$-$C_6)$-alkyl, CON(R40)(R41) or CO(R42);

R40, R41 and R42 are each independently H or $(C_1$-$C_8)$-alkyl;

or

R40 and R41 taken together with the nitrogen atom to which they are attached form a 5-6-membered ring which, apart from the nitrogen atom, may also include 0-1 further heteroatoms selected from the group consisting of NH, N—$(C_1$-$C_6)$-alkyl, oxygen and sulfur;

X is C(R43)(R43');

R6, R6', R7, R7', R43 and R43' are each independently H, F, $(C_1$-$C_8)$-alkyl, OH, or O—$(C_1$-$C_6)$-alkyl;

or R6 and R6', or R43 and R43' together are oxo;

R8 is H or $(C_1$-$C_8)$-alkyl;

L2 is a bond or C(R44)(R45);

R44 and R45 are each independently H or $(C_1$-$C_8)$-alkyl;

A is a 5-6-membered aromatic ring that may include up to two heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, and is optionally substituted by one or more of substituents selected from H, F, Cl, Br, I, OH, CF_3, NO_2, CN, OCF_3, O—$(C_1$-$C_6)$-alkyl, O—$(C_1$-$C_4)$-alkoxy-$(C_1$-$C_4)$-alkyl, $(C_1$-$C_6)$-alkyl, N(R54)(R55), SO_2—CH_3, CON(R56)(R57), N(R58)CO(R59), and CO(R60);

provided that when L2 is a bond, then C(O)NR8 may be joined to an ortho substituent of A via a bridge containing one or two elements from the group of carbon and nitrogen, so as to form a 9- to 10-membered bicyclic ring overall;

R54, R55, R56, R57, R58, R59, and R60 are each independently H or $(C_1$-$C_8)$alkyl;

or

R54 and R55, and R56 and R57 each independently taken together with the nitrogen atom to which they are attached form a 5-6-membered ring which, apart from the nitrogen atom, may also include 0-1 further heteroatom from the group of NH, N—$(C_1$-$C_6)$-alkyl, oxygen and sulfur;

L3 is C(R62)(R63)O, and

B is a 4- to 10-membered mono-, bi- or spirocyclic non-aromatic ring that includes from 1 to 3 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur, wherein the non-aromatic ring is optionally substituted by one or more substituents selected from F, CF_3, $(C_1$-$C_6)$-alkyl, O—$(C_1$-$C_8)$-alkyl, $(C_1$-$C_4)$-alkoxy-$(C_1$-$C_4)$-alkyl, hydroxy-$(C_1$-$C_4)$-alkyl, oxo, CO(R64), and hydroxyl; and

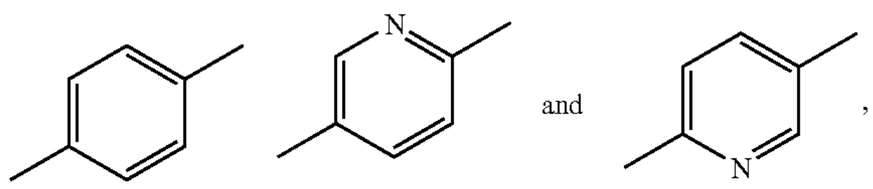
R62, R63, and R64 are each independently H or $(C_1$-$C_8)$-alkyl;

or a physiologically compatible salt thereof.

2. The compound according to claim **1**, wherein L2 is a bond.

3. The compound according to claim **1**, wherein R1 and R2 taken together with the nitrogen atom to which they are attached form a 4- to 10-membered mono-, bi- or spirocyclic ring which, apart from the nitrogen atom, may include from 0 to 2 additional heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur, wherein the ring is optionally substituted by F, Cl, Br, CF_3, $(C_1$-$C_6)$-alkyl, O—$(C_1$-$C_8)$-alkyl, $(C_3$-$C_8)$-cycloalkyl, $(C_1$-$C_4)$-alkoxy-$(C_1$-$C_4)$-alkyl, hydroxy-$(C_1$-$C_6)$-alkyl, oxo, CO(R18), hydroxyl, N(R22)CO$(C_1$-$C_6)$-alkyl, or $SO_2(C_1$-$C_6)$-alkyl.

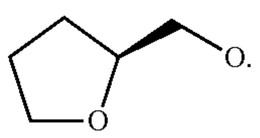
4. The compound according to claim **1**, wherein A is selected from the group consisting of



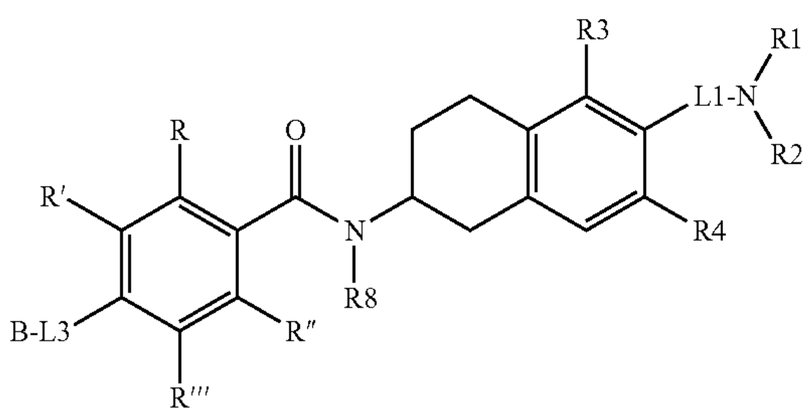
any of which is optionally substituted by one or more of substituents selected from H, F, Cl, Br, I, OH, CF_3, NO_2, CN, OCF_3, O—(C_1-C_6)-alkyl, O—(C_1-C_4)-alkoxy-(C_1-C_4)-alkyl, (C_1-C_6)alkyl, N(R54)(R55), SO_2—CH_3, CON(R56)(R57), N(R58)CO(R59), and CO(R60).

5. The compound according to claim **1**, wherein B is a 4- to 6-membered non-aromatic ring that includes from 1 to 2 oxygen atoms, wherein the ring is optionally substituted by one or more substituents selected from (C_1-C_6)-alkyl and hydroxyl.

6. The compound according to claim **1**, wherein the moiety B-L3 is



7. The compound according to claim **1**, which is a compound of formula II



wherein:

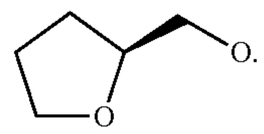
L1, R3, R4 and R8 are each as defined in claim **1**;

R, R', R" and R"' are each independently selected from the group consisting of H, F, Cl, Br, I, OH, CF_3, NO_2, CN, OCF_3, O—(C_1-C_6)-alkyl, O—(C_1-C_4)-alkoxy-(C_1-C_4)-alkyl, (C_1-C_6)-alkyl, N(R54)(R55), SO_2—CH_3, CON(R56)(R57), N(R58)CO(R59), and CO(R60);

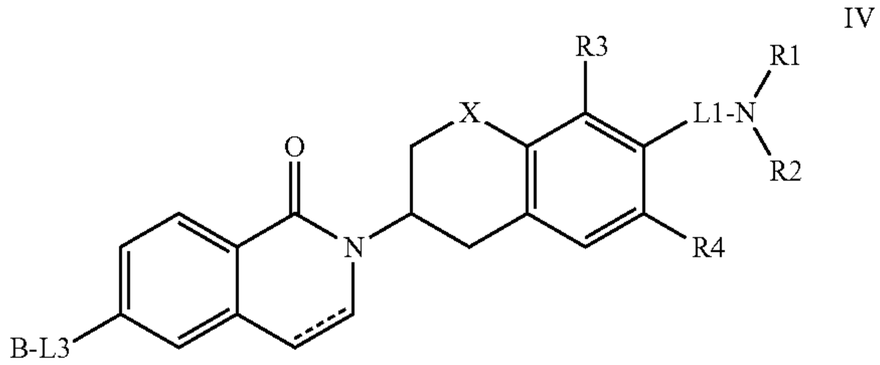
L3 is CH_2O; and

B is a 4- to 6-membered non-aromatic ring that includes from 1 to 2 oxygen atoms, wherein the ring is optionally substituted by one or more substituents selected from the group consisting of F, (C_1-C_6)-alkyl, O—(C_1-C_8)-alkyl, (C_1-C_4)-alkoxy-(C_1-C_4)-alkyl, oxo, and hydroxyl.

8. The compound according to claim **7**, wherein the moiety B-L3 is



9. The compound according to claim **1**, which is a compound of formula IV



wherein R1, R2, R3, R4, X, L1, L3 and B are each as defined in claim **1**, and the broken line indicates an optional double bond.

10. A pharmaceutical composition comprising the compound according to claim **1** or a physiologically compatible salt thereof, in combination with a pharmacologically acceptable carrier or excipient.

11. The pharmaceutical composition according to claim **10**, further comprising one or more active ingredients effective in treating a metabolic disorder or a disease associated therewith.

12. The pharmaceutical composition according to claim **10**, further comprising one or more anti-diabetics.

13. The pharmaceutical composition according to claim **10**, further comprising one or more lipid modulators.

14. The pharmaceutical composition according to claim **10**, further comprising one or more anti-obesity agents.

15. A pharmaceutical composition comprising the compound according to claim **7** or a physiologically compatible salt thereof, in combination with a pharmacologically acceptable carrier or excipient.

16. A pharmaceutical composition comprising the compound according to claim **8** or a physiologically compatible salt thereof, in combination with a pharmacologically acceptable carrier or excipient.

17. A pharmaceutical composition comprising the compound according to claim **9** or a physiologically compatible salt thereof, in combination with a pharmacologically acceptable carrier or excipient.

18. A process for preparing a pharmaceutical composition comprising the compound according to claim **1** or a physiologically compatible salt thereof, in combination with a pharmacologically acceptable carrier or excipient, comprising mixing the compound according to claim **1** or the physiologically compatible salt thereof with the pharmacologically acceptable carrier or excipient, and converting the mixture into to a form suitable for administration.

19. The compound according to claim **1**, wherein A is a 5-6-membered aromatic ring optionally substituted by one or more substituents selected from H, F, Cl, Br, I, OH, CF_3, NO_2, CN, OCF_3, O—(C_1-C_6)-alkyl, O—(C_1-C_4)-alkoxy-(C_1-C_4)-alkyl, (C_1-C_6)-alkyl, N(R54)(R55), SO_2—CH_3, CON(R56)(R57), N(R58)CO(R59), and CO(R60).

* * * * *